CHAPTER 1

General introduction
This thesis consists of a collection of studies that were conducted in outpatient mental health clinics. The main focus is on Internet-based treatment for depression in routine mental health care. The thesis contains: the results of an observational study, a randomized controlled trial (RCT) that was conducted in an effort to examine the effects of Internet-based Problem Solving Treatment (PST) in regular outpatient clinics, the results of a naturalistic study of the costs and effects of blended treatment in outpatient clinics, and the results of a study that examined predictors of outcome in self-guided Internet-delivered Cognitive Behavior Treatment (CBT). This first chapter provides a general introduction to the contents of this thesis.

**Common mental disorders**

Depressive disorders and anxiety disorders are common and disabling mental disorders. Together they affect 700 million people worldwide each year [1, 2]. Both depression and anxiety are associated with severe losses in quality of life and psychosocial functioning, and are accompanied by high healthcare costs [3]. Consequently, this makes the demand for effective treatment for anxiety and depressive disorders high.

Depression is an affective disorder that is characterized by persistent depressed mood and/or a loss of interest or initiative not fully explained by circumstances. Other symptoms include: a change in psychomotor activity, sleep and appetite disturbances, loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate and/or recurrent thoughts of death or suicide ideation. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [4, 5] - which was used during the time the studies of this thesis were conducted - the diagnosis major depressive disorder (MDD) is made if at least five of the before mentioned symptoms have been present during the same two-week period, with at least one of the symptoms being either 1) depressed mood or 2) loss of interest or initiative. Additionally, the symptoms cannot be due to direct physiological effects of substances or general medical conditions. The symptoms cause significant distress or impairment in social, occupational or other important domains of functioning [5] and represent a change from previous functioning. In the new version of the DSM (DSM-5), neither the core criterion symptoms applied to the diagnosis of MDD, nor the requisite duration of at least 2 weeks has changed from DSM-IV.
It is estimated that depression currently affects 350 million people worldwide [6], which makes it the fourth disorder in terms of disease burden. By 2030 depression is expected to rank first in disease burden in high-income countries [7]. Because it affects people in all communities across the world, reduces daily functioning and is often recurring, it is currently the leading cause of disability measured in YLDs (years lived with disability) [7].

The most recent study examining the prevalence of MDD in the Netherlands (Nemesis-2) showed that 5.8 percent of the Dutch population (approximately 589,000 people) suffers from MDD every year and about 19 percent of the Dutch population fulfill the criteria of MDD at least once in their lives [8]. Depression is responsible for an annual loss of 157,700 disability adjusted life years (DALYs) in the Netherlands [9]. The reduction of quality of life for patients with depression is even more than in other health conditions such as diabetes, lung cancer and dementia. Furthermore, depression is associated with increased healthcare utilization and high costs [3, 10]. The costs related to depression include direct costs, such as medical costs and patients ‘out-of-pocket expenses, as well as indirect costs, due to decreased work performance (presenteeism) and/or absence from the workplace (absenteeism) [11, 12]. Overall, the annual costs of depression in the Netherlands are estimated at nearly three billion euro [13].

Anxiety disorders, like depressive disorders, are among the most prevalent psychiatric disorders in the world, with estimated lifetime prevalence rates of up to 29% [14]. Anxiety disorders include a wide range of different disorders in the DSM-IV [5] (e.g. generalized anxiety disorders, social phobia, post-traumatic stress disorder (PTSS), obsessive compulsive disorder (OCD), panic disorder with or without agoraphobia, and specific phobias) and are characterized by symptom clusters around excessive worrying and irrational fear. In the chapter on anxiety disorder in the DSM-5 [5] obsessive-compulsive disorder and posttraumatic stress disorder are no longer included, but are included in separate chapters: obsessive-compulsive and related disorders and trauma- and stressor-related disorders, respectively. Another change from DSM-IV is that panic disorder and agoraphobia are unlinked in DSM-5 and are now replaced by two diagnoses, panic disorder and agoraphobia, each with separate criteria.

Anxiety disorders are the sixth leading cause of disability, in terms of YLDs, in high-, low- and middle-income countries [7] and are, like depression, also associated with substantial costs for the individual and society [3].
Psychological treatment of depression and anxiety

With their high prevalence, high burden of disease and substantial economic consequences, the treatment of depression and anxiety is important. Current national and international guidelines recommend pharmacological treatments and/or psychological therapies for the treatment of depression and anxiety [15-18]. Pharmacological treatments include Tricyclic Antidepressants (TCA’s), Selective Serotonin Reuptake Inhibitors (SSRI’s), Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRI’s) [19]. These treatments work for many patients [20], however relapse is high when patients discontinue taking medication and in Western societies most patients prefer psychological treatments over pharmacological treatments [21, 22].

Psychological treatments for depression and anxiety have been examined in over four hundred randomized controlled trials [23]. The evidence supports the effectiveness of many treatment models for depression ( e.g. Cognitive Behavioural Therapy (CBT) [24], Interpersonal Psychotherapy (IPT) [25] and Problem Solving Therapy (PST) [26]). The most common psychological therapies seem to be equally effective for depression [23]. Furthermore, the effects are comparable to those found in pharmacotherapy studies [27] and there is no evidence that psychotherapies are less effective in severe depression [28]. The combination of pharmacotherapy and psychotherapy is significantly more effective than either treatment alone [29].

For the treatment of anxiety, psychological treatments like CBT with exposure in vivo (for social anxiety, generalized anxiety, and specific phobias), CBT with Exposure Response Prevention Therapy (ERP) (for OCD), Eye Movement Desensitization and Reprocessing (EMDR) and Trauma-focused CBT (for PTSS) are recommended in (inter)national guidelines, either with or without pharmacotherapy [71].

Despite the proven effectiveness of different treatments, depression and anxiety disorders often remain untreated. Rates of treatment seeking are low [30] and when patients do seek treatment the treatments are not easily accessible [31]. Due to scarce health care resources, limited availability of trained clinicians, long waiting lists, stigma and costs related to treatment, less than half of individuals with mental disorders receive treatment. This is even less in adolescents, older adults and individuals with lower socioeconomic status and from ethnic minorities [32-34]. The need for a further reduction of the disease burden of common mental disorders is high [31], but several of the before mentioned issues pose a barrier to the uptake of effective treatments.
Regular psychological treatment, delivered in individual face-to-face sessions, is an expensive mode of therapy delivery and takes up a lot of clinician time and other resources. With the current prevalence rates of depression and anxiety disorders, there is a high demand for psychological treatment, but too little supply. In addition, the national health care budget in the Netherlands is shrinking, which has a major impact on the resources for mental health care and puts pressure on mental health care providers to offer both (cost-)effective and efficient treatments.

Internet delivered treatments are often proposed as both an effective and an efficient approach to reduce the costs of treatment. The proposed benefits of treatment delivery via the Internet are that it allows for more patients to receive psychological treatment, thereby improving access to treatment, and it has the potential to create more treatment options within the mental health care system at relatively low costs.

**Internet-delivered treatment**

Internet-delivered treatments make use of the same principles as traditional face-to-face treatment. The difference is that the therapeutic content is provided via the Internet on computers, tablets or smartphones. In most Internet treatments evidence-based psychological treatment models are used as a framework (e.g. CBT) and are then adjusted for Internet delivery. The structure of the Internet interventions is similar to that of regular face-to-face treatments; content and assignments are dispatched in (weekly) sessions and the goal is that patients will practice and apply the techniques in their daily lives. Most Internet interventions provide text-based information and are highly structured with systematically presented psycho-education, (homework) assignments and other resources (e.g. activity monitoring, electronic (thought) diaries) [35].

Internet interventions can be provided with some level of contact with a clinician or coach via (asynchronous) email or a secure messaging system within the intervention platform, or via (synchronous) online chat or telephone calls. The guidance that is offered, is usually meant to help users get through the intervention, to enhance motivation and to make sure users understand the presented techniques and assignments. Internet interventions can also be entirely self-guided [36]. In that case, the users are expected to work through the intervention by themselves and receive no feedback on (homework) assignments.

Internet-based psychological treatments are considered to have great potential to reduce the burden of disease of common mental health disorders [23, 37, 38]. The advantages
of Internet treatments include convenience - as patients can access and re-read treatment material anytime, anywhere [39] -, potentially lower costs - as internet treatment usually take up less clinician time and resources [40-44]-, and the opportunity to treat more patients - as training burden and clinician time decreases, relative to traditional face-to-face treatments [45]. Moreover, patients gain faster access to treatment as they can start with Internet treatment immediately after entering the healthcare system.

Many studies have confirmed the efficacy of Internet treatments in treating individuals with either clinical or subclinical symptoms of depression and anxiety [32, 46-48]. There is now even evidence that Internet interventions with clinician guidance can be as effective as face-to-face treatments [49, 50] and evidence that these interventions are potentially cost-effective for anxiety and depression [41, 43, 51, 52].

**Internet treatment in routine mental healthcare**

The advantages of Internet-based treatments described above, highlight the public health potential of (guided) Internet interventions as methods for increasing access to evidence-based treatment, to shorten or even undo waiting lists and to offer cost-effective treatments to those in need. Internet-interventions could be useful when offered in outpatient clinics, for example during the waitlist period, in blended format with both online as face-to-face consultations, and/or in specialized virtual clinics where solely Internet treatment is offered.

The first option, offering guided Internet treatments during the waitlist period, corresponds well with stepped care models as proposed by the NICE guidelines of the National Institute for Health and Clinical Excellence in England and Welch [53] for the treatment of depression and anxiety. The general principle behind stepped-care models is that patients start with the treatment of lowest intensity, and step up to more intensive treatment if needed [54, 55]. The national guidelines in the Netherlands align with such stepped-care recommendations. As Internet-based guided self-help interventions are often described as low intensity in terms of clinician involvement, they might suit well as a first step of treatment. When Internet treatment during the waitlist proves to be effective, it can give patients a head start in treatment or even cancel out more intensive (face-to-face) treatment when patients make full recovery.

The second option, blended care, is viewed as another promising way of treatment delivery as it is presumably less disruptive to healthcare organizations and more acceptable for clinicians, compared to stand-alone Internet treatments. The advantages of blended care
include all the benefits of Internet treatment, while the face-to-face sessions ensure that clinicians can respond to the patients’ more complex problems during face-to-face sessions.

The third option, standalone Internet treatment, can be offered with or without additional guidance. The treatment however, solely takes place via the Internet while guidance can be offered either by secured emails, chats, skype or telephone calls. In standalone Internet treatment the patients will not physically meet the therapist, and have to work through the materials by themselves.

Because of the relatively new mode of treatment delivery challenges remain with respect to implementation of Internet treatments in routine care. First of all, not much research has examined whether Internet treatments are acceptable for patients who seek treatment in regular outpatient mental health clinics. Those patients might be more severely depressed and therefore less motivated to adhere to Internet treatments in which they need to work quite independently. Second, despite enthusiasm for the potential ease of dissemination, not much research has examined the effects of Internet-based treatment in clinical populations in regular outpatient clinics. Previous studies have primarily demonstrated the efficacy of Internet-based treatments among self-referred participants with elevated or (sub)clinical symptoms, recruited from the general population. These studies show that guided Internet-based treatments are effective for depression and depressive symptoms [46, 47, 60-62], panic disorder [63-65], social phobia [66-68], generalized anxiety disorder [69, 70] and specific phobia [71], among others. However, these results may not generalize to patients diagnosed with a depressive or anxiety disorder, who are seeking treatment in regular outpatient clinics. A common finding in Internet RCT’s is that the research population often is highly educated. This might play a role in responsiveness to Internet-based treatments, as increased levels of education and self-referral to Internet trials might increase levels of motivation and adherence to Internet treatment. There is not much research on patient characteristics in Internet treatments recruited via self-referral versus other trials and outpatient clinics, however there is some evidence that suggests that participants in Internet trials are more similar to the general population than to patients in outpatient clinics [72, 73]. The effectiveness of Internet treatments in regular outpatient clinics for patients with a mental health disorder need to be studied before large scale dissemination of these treatments. Third, it is not known if clinicians are willing and able to administer Internet-based treatments. Clinicians are extensively trained in providing face-to-face treatment. The use of Internet interventions requires clinicians to alter their usual therapeutic methods. Implementing Internet treatments may encounter barriers to the dissemination. Barriers may arise at the patient, clinician or
organisational level. Clinician barriers can for example be practical (e.g. lacking skills to provide Internet treatment) and attitudinal (e.g. seeing Internet treatment as second-rate treatment). Clinicians may fear losing their work as practicing therapists if Internet interventions are disseminated. This is however not likely to happen, given the large number of people in need of treatment and the shortage of trained therapists. Nonetheless, Internet-based treatments will have limited impact on mental health care if they are not acceptable and effective for patients in regular outpatient care and if clinicians or outpatient clinics are not able to administer the treatment. Fourth, as Internet interventions often require less therapist time and resources, they have the potential of being more cost-effective than traditional psychological treatments. However, the (cost)-effectiveness of Internet treatments in outpatients clinics is not well studied yet. Fifth, there is not much knowledge about the characteristics of participants who are likely to benefit from Internet treatments. There is very little empirical data to guide conclusions about which variables and patient characteristics are associated with outcomes in Internet-delivered interventions. Several studies have examined a wide range of potential predictors of clinical response as a way of understanding the characteristics of participants who benefit from Internet interventions, but results are inconsistent and more research is needed. Furthermore it seems not very likely that Internet treatment is the best treatment for all patients. Research is needed to guide conclusion for whom Internet treatments are the most beneficial.

In sum, many questions about effectiveness and implementation of Internet interventions in outpatient clinics still need to be answered. It is necessary to examine whether Internet interventions are acceptable for patients and clinicians in regular outpatient clinics, whether these interventions are (cost)-effective and which variables and characteristics are associated with outcome of Internet treatments.

**Internet-based) Problem Solving Treatment**

Problem-Solving Therapy (PST) is psychological treatment that focuses on training in adaptive problem-solving attitudes and skills. Several studies have shown the effectiveness of conventional PST for depression as well as for symptoms of anxiety [56, 57]. There are several types of PST. The first type, ‘social problem-solving therapy’ (SPST) [78] focusses on problems solving skills and on changing dysfunctional attitudes or beliefs that inhibit or interfere with attempts to engage in the problem-solving tasks. The second type, PST for primary care (PST-PC) [79], focuses on the core elements of problem-solving and is designed
to be administered by trained nurses. The third type of problem-solving, self-examination problem solving treatment [74, 75], is aimed at 1) identifying important things in life, 2) thinking less (negatively) about things that do not relate to those important things in life 3) investing energy in things that are important and 4) learning to accept those problems that cannot be changed. Self-examination PST is typically used in a guided self-help format, however it can also be applied in group or individual settings. The advantages of this type of PST is that it is a generic intervention that can be easily altered to apply to different mental disorders [75]. The treatment is an element used in cognitive behavior therapy and encourages individuals to think more adaptively. The unique features of this intervention include that individuals need to spend 30 minutes a week to think only about what matters to them (identify their main values) and that the intervention was designed to be a self-administered treatment.

In the studies in chapter 2, 3, 4 and 5 of this dissertation, self-examination PST (hereafter referred to as PST) was adjusted for Internet delivery and examined. This Internet-based intervention is named ‘Taking Control’ (original title: Alles Onder Controle) and is a short, structured and generic intervention consisting of five weekly sessions. The generic character of the Internet PST makes it suitable to address different kinds of symptoms. This is useful because of the high prevalence of comorbidity in psychiatric disorders [76]. The Internet-based PST has proved to be effective in reducing symptoms of depression and anxiety in community samples [58, 59].

The intervention sets out to teach skills which help patients to regain control over their problems. During the Internet-based intervention patients learn to determine what really matters to them (session 1), and are offered structured strategies to solve those problems that are related to what matters (session 2, 3 and 4). Furthermore attention is paid to thinking less negatively about the unimportant problems (session 3), and to learn to accept those situations that cannot be changed (session 4). The main focus is on adopting a structured six-step approach when encountering important, potentially solvable problems. This structured approach consists of: identifying the problem; identifying as many solutions as possible; selecting one of those solutions; creating a plan to execute the chosen solutions; the actual execution of this plan and, finally, evaluating the results. The last week of the intervention (session 5) is reserved for both the reflection on long-term goals and the development of a structure to achieve these goals. Each Internet session contains structured homework assignments on which the participants receive weekly online feedback from a coach. The feedback is of a non-therapeutic nature and aims to help participants to become familiar with
the presented techniques. Because of the generic character of this intervention and the minimum amount of therapist time needed, this intervention was chosen a first step of treatment during the waitlist in outpatient mental health clinics.

**Objectives and outline of this thesis**

Clinical effectiveness and cost-effectiveness are important when evaluating whether a new way of treatment delivery should be implemented into clinical practice. This dissertation examines the (cost)-effectiveness of Internet-based PST during the waiting list in outpatient clinics, the effects and costs of blended CBT in outpatient clinics and predictors of outcome for self-guided Internet delivered CBT for the general population.

**Chapter 2** presents the findings of an observational study that was executed in a regular outpatient mental health clinic. The clinic had implemented Internet-based PST in their standard care and offered it during the waitlist period. The study reports on the uptake of the Internet treatment, the demographic and clinical variables of patients who preferred online treatment, and the change in symptoms. **Chapter 3** contains the rationale for the randomized controlled trial, states the research questions and describes the study design and procedures. **Chapter 4** examines the clinical effectiveness of Internet-based PST for depressed outpatients and reports on the short-term effects. **Chapter 5** examines whether starting with Internet-based PST during the waitlist in outpatient clinics results in less uptake of face-to-face sessions. The study reports the long term clinical outcomes and cost-effectiveness of Internet-based PST in outpatient clinics. **Chapter 6** presents the results of a naturalistic study that evaluates the costs and effects of blended treatment in routine mental health care for patients with depression or anxiety disorders. The aim of the study in **Chapter 7** is to explore demographic characteristics, clinical characteristics and several therapy related variables as predictors of treatment response to self-guided Internet-delivered treatment for symptoms of anxiety and depression. **Chapter 8** provides the general discussion of the main findings and methodological considerations and limitations of the studies. The thesis is concluded with a summary in **Chapter 9**.
References


