1. Introduction
As stated in chapter 1, this study is carried out because patients and their care-givers have much to gain by the development and implementation of effective care for patients on sick leave having stress-related mental disorders (SMDs). Most people having SMDs with sick leave consult their general practitioner (GP) at an early stage. Currently, few evidence-based therapies exist to help patients to cope and to prevent sick leave, and general practice lacks a guideline with a structured treatment plan. We developed a minimal intervention to help GPs diagnose and treat patients having SMDs with sick leave.

2. Stress and coping in relation to common mental disorders and the MISS
In chapter 2, we argue that the concept of stress-related disorders does not fit the existing diagnostic classification systems (such as the DSM-IV and the ICD-10), but may be most applicable when no formal psychiatric disorders are diagnosable. It may be viewed as an important dimension of mental disorders that cuts across all established diagnostic categories. In the Minimal Intervention for patients having SMDs with Sick leave (MISS), GPs focus on the first stage of the breakdown. After the ‘crisis’ a patient experiences, patients need to regain control and start coping again. Otherwise, the long-lasting sick leave could have severe consequences like loss of employment, social marginalisation and permanent disability. Through the use of relatively simple, empowering interventions such as education, support, advice and homework assignments, the intervention specifically aims at damming avoiding tendencies and at promoting an active approach of psychosocial problems.

3. Design
Chapter 3 provides a description of the setting and design of our MISS, and confirms compliance with the requirements for a cluster Randomised Controlled Trial (RCT). Our hypothesis was that the MISS is more effective compared to usual care (UC) in reducing days of sick leave of these patients. Randomisation was at the level of GPs, they received the MISS training versus no training, in order to compare the MISS vs. usual care at patient level. Enrolment of participants took place after screening the source population, which comprised 20-60 year old primary care attendees. Enrolment criteria were: moderately elevated distress levels, having a paid job and sick leave for no longer than three months. Primary outcome measure after one year follow-up was lasting full return to work. Reduction of SMD symptoms was one of the secondary outcome measures. Forty-six GPs and 433 patients agreed to participate.

4. Effectiveness of the MISS
Chapter 4 presents the effects of our MISS versus UC. There was no evidence that the MISS was superior to UC within the total group on our primary outcome measure days of sick leave (HR 1.06, 95% CI 0.87 – 1.29). The median number of days on sick leave before return to work was substantial (MISS 96 days and UC 102 days). Subgroup analyses showed effectiveness of MISS over UC on days on sick leave for the subgroup, SMDs (HR 1.72, 95% CI 1.18- 2.51). The severity of symptoms reduced significantly in both groups during follow up. Nevertheless, a considerable amount of patients after 1 year still scored above threshold on the self-reported symptoms. Diagnosing SMD turned out to be less straightforward than
we expected and the evidence-base on effectiveness of the MISS has to grow substantially before definitive conclusions can be drawn.

5. Cost-effectiveness of the MISS
Chapter 5 presents the cost-effectiveness of our MISS compared to UC. The economic evaluation was performed alongside our cluster RCT and conducted from both societal and company perspective with a follow up of one year. Outcomes were the number of sick leave days beginning from the first day of sick leave to 1-year thereafter, quality adjusted life years, resource use, investment costs and productivity loss costs.

In total, 192 (44%) complete cases were available. There were no significant differences in outcomes or costs. The incremental costs per day less of gross sick leave was €33, and per quality adjusted life years €76,046. The potential cost offset ranged from a loss of €135 to a savings of €1,369. Results of sensitivity analysis were similar to the main findings for the total group. With respect to the SMD subgroup, cost-effectiveness of MISS over UC was indicated. Those in the MISS group incurred significantly less gross and net sick leave days than UC (mean gross difference 74.0 days, 95% CI 14.7 – 132.9). While the MISS was not associated with a superior clinical or economic impact than usual GP care for a heterogeneous population with symptoms of SMD, it may be a promising intervention for the subgroup, patients diagnosed with SMD.

6. Performance of the general practitioners
The aim of chapter 6 was to evaluate the potential differences between the MISS and UC in application of treatment-components. Elements in the MISS were: assignment of a correct diagnosis, providing information and advice, monitoring the symptoms and, if necessary, referral to more extensive care. Twenty-four GPs were randomly assigned to the MISS-group, 23 of whom completed the 11-hour MISS training. Information on application of the treatment components was derived from questionnaires filled in by both the GP and patients, and from the electronic medical record of the patient. Differences in favour of the MISS group were found for several elements of the MISS. A psychological diagnosis was more frequently diagnosed by the GPs in the MISS group than by the GPs in the UC group (78.1% versus 67.4%, p=0.020). Furthermore, the GPs in the MISS group more often used a mental health questionnaire (the 4DSQ) (16.1% vs. 1.3%, p=0.000), handed out information leaflets (28.3% vs. 10.8%, p=0.001) and knew how the patients are doing two months after baseline (76.4% vs. 65.7%, p=0.041). The treatment components advice and referral did not show significant differences between MISS and UC. In conclusion, GPs can be trained to successfully apply at least some of the elements of the MISS intervention.

7. Test-retest reliability of the PRIME-MD
In chapter 7, test-retest study of the Primary Care Evaluation of Mental Disorders (PRIME MD) is described. The PRIME-MD is one of the few instruments in primary care that actually diagnoses specific mental disorders according to the DSM criteria. One-hundred distressed patients (20-60 years old) who were on sick leave were interviewed, with one-week interval. Almost everyone (89%) received one or more diagnoses at both measurements, and there was fair total agreement (κ .27). The best agreement was found for more severe threshold disorders (major depressive disorder [κ .58], dysthymia [κ .57], and generalised anxiety disorder [κ .59]), while agreement for the sub-threshold disorders was not satisfactory
(anxiety disorder not otherwise specified [NOS] [κ .30], minor depressive disorder [κ -.03], and somatoform disorder NOS [κ .11]). Mental disorders, as seen in primary care, encompass important specific symptoms and clinical syndromes that vary in duration and severity over time, but they also encompass an admixture of somatic and psychological symptoms that do not match current diagnostic systems. This probably contributes to the overly inclusiveness of threshold disorders and the failure to adequately classify sub-threshold disorders with the PRIME-MD. In conclusion, diagnostic criteria in psychiatry need to be operationalised for use in primary care and require further evaluation.

8. General discussion
In chapter 8, some important issues and considerations covering the foregoing chapters were discussed. The findings presented in this thesis are a first step and many of the issues discussed remain unclear. The results showed no evidence that the MISS was superior to UC on the total group level. Subgroup analyses showed effectiveness and cost-effectiveness of MISS over UC on days of sick leave for the patients that actually were diagnosed by their GP as having a SMD. This suggest that the MISS as an activating intervention is a promising approach for patients suffering from psychopathology which are sub-acute, not chronic and clearly related to stress (e.g. SMD, adjustment disorder, neurasthenia, nervous breakdown), but so far the MISS is not the way out for preventing disability in patients with psychological problems. The research agenda on patients having (symptoms of) SMDs with sick leave should include the evaluation of methods to define and assess disease and disability, and patients characteristics should be evaluated for fine-tuning the necessary elements of the MISS. Considering these needs, only studying effectiveness with a randomised controlled trial may seem insufficient. Also qualitative research on the above mentioned factors involved in SMD symptoms and sick leave is recommended. Implications of our study for daily general practice are not completely straightforward, yet practice lies ahead of evidence base since some elements form the MISS already are implemented. And in conclusion, these developments in practice certainly are positive and worth structural support by training and education, since they reflect a step forward in a field that not yet has but clearly needs more well defined and structured care.