Summary
Summary

Chapter 1

This chapter introduces the topic of the thesis: the diagnosis and prognosis of patients who present with unexplained complaints in general practice, with special attention for the role of blood test ordering. In this thesis we defined unexplained complaints as the Dutch College of General Practitioners (DCGP) did in its guideline on blood test ordering: ‘Complaints for which the GP cannot establish a specific diagnosis after history taking and physical examination’. 3-39% of the consultations in general practice concern unexplained complaints, and 90% of these complaints were no reason for patients to revisit their GP within a month, which in literature is taken to mean that the complaints were self-limiting. Because unexplained complaints may in time turn out to be the symptoms of various diagnoses, there is a diagnostic uncertainty for the GP, which can trigger him or her to order blood tests. However, there are various arguments to be cautious with additional blood test ordering in this group of patients. The chapter continues to discuss the expected pros and cons of two blood test ordering strategies, that is immediate and postponed blood test ordering. In the presence of a low prior risk of serious somatic disease there is a relatively high risk of false positive test results when ordering blood tests immediately. False positive test results in turn may lead to a cascade of unnecessary further tests, referrals and treatments, as well as to anxiety and even somatisation. Therefore, in its guideline on blood test ordering, the DCGP advises to postpone blood test ordering for four weeks for patients presenting with unexplained complaints for the first time and to restrict the number of test ordered. Little is known, however, about patients with newly presented unexplained complaints in general practice and about the transition of these complaints into established complaints. Especially the diagnostic value of (postponed) blood test ordering, and the course of newly presented unexplained complaints in terms of persistence over time, quality of life and its determinants, need clarification. For this reason, we have developed the Vague Medical Problems In REsearch (VAMPIRE) trial with the following research questions:

1. What are the characteristics (in terms of demographics and quality of life) of patients presenting with unexplained complaints in general practice?

2. How many and which blood tests are ordered by GPs for patients with unexplained complaints in general practice?

3. What are patient and consultation-related determinants of GPs’ decisions to order blood tests immediately for patients presenting with unexplained complaints in general practice?
What is the yield of blood test ordering for patients presenting with unexplained complaints in general practice in terms of established diagnoses/evaluations after 12 months of follow-up and the occurrence of abnormal test results among patients with these complaints, either when tests are ordered immediately or postponed?

What is the effect of a four-week postponement of blood test ordering on patients’ anxiety and satisfaction, compared to an immediate test ordering strategy?

What is the course of unexplained complaints in terms of the presence of complaints over time and complaint-related diagnoses?

What are determinants of patients at risk for developing persistent (established unexplained) complaints and determinants of the course of the quality of life of patients presenting with unexplained complaints?

Chapter 2

The special methodological challenges of diagnostic research among patients who present with unexplained complaints in general practice are described in chapter 2. The origin of several of these challenges is the concept of the unexplained complaint itself, which is not unequivocally defined. As a consequence this creates difficulties in selecting the proper study population, in defining accurate reference standards and in defining useful outcome measures. Although several of the individual obstacles apply to research into other complaints as well, their combination is characteristic of research into unexplained complaints. This might be one of the reasons why such research has been scarce and why there is need for more adequate methodology.

Chapter 3

The VAMPIRE trial was set up as a randomised clinical trial to evaluate the effects of immediate versus postponed blood test ordering for patients presenting with unexplained complaints in general practice. The trial had three main objectives. First, to determine the accuracy of blood tests in patients presenting with unexplained complaints; secondly, to determine the value of postponing blood test ordering and thirdly to determine the effects of a quality improvement strategy in terms of promoting the postponement of blood test ordering by GPs in these patients. The protocol of the trial is presented in this chapter. Participating general practices were randomized into three groups. GPs from group 1 were instructed to order blood tests immediately, and GPs from groups 2 and 3 were asked to postpone blood test ordering for patients presenting with unexplained complaints. In addition, group 3 was supported in postponing blood test ordering by a systematically developed quality improvement strategy. Patients with unexplained fatigue, abdominal complaints,
musculoskeletal complaints, weight changes and itch were eligible for inclusion. The investigated blood test sets concerned both traditional and innovative tests. The quality improvement strategy consisted of two small-group meetings and a practice outreach visit. Patient follow-up ended 12 months after the initial complaint presentation. The innovative aspect of this trial was that it combined a clinical epidemiology trial and a quality-of-care study. Van Bokhoven discusses the third, and parts of the second objective of the trial in a parallel thesis, written at Maastricht University, the Netherlands.

Chapter 4

Before the actual start of the trial, we investigated potential patient and consultation-related determinants of GPs’ decisions to order blood tests and the number and kind of tests ordered. In this cross-sectional study, 27 Dutch GPs completed standardized registration forms immediately after consultations with patients who presented with unexplained complaints. Data of 100 patients were analysed. Fifty-nine patients had at least one blood test ordered. The median number of ordered tests was 10 (inner percentile range 90 (ipr90) 2-15). Compared to abdominal complaints, the test-ordering probability for fatigue as type of complaint was five times higher (RR 5.2; 95%CI 2.5 to 6.1). Duration of the complaint for over four weeks increased the likelihood by 1.6 times (RR 1.6; 95%CI 0.8 to 2.2). Factors associated with a lower test ordering probability were the likelihood of background psychosocial factors (RR 0.4; 0.03-1.1) and a syndrome, rather than a symptom, type of working hypothesis of the GP (RR 0.5; 0.2-0.9). Based on these results, the chapter concludes that the selectivity in blood test ordering behaviour of GPs can be improved upon. However, the absence of modifiable determinants in our findings limits their direct use for action. The chapter ends to conclude that to improve rational blood test ordering in general practice, more information is needed on the added value of blood test ordering in the work-up of patients with unexplained complaints.

Chapter 5

Chapter 5 describes and compares the demographic characteristics and quality of life of the participants of the VAMPIRE trial at presentation. Little is known about these characteristics in patients with newly presented unexplained complaints. In this descriptive part of the study, the demographic characteristics of our study population were compared to a Dutch general practice population. Quality-of-life scores were measured with the RAND-36 and compared to another Dutch general practice population and to depressed patients. Data of 466 patients were available for analysis. Mean age was 44 years and 74% were female, mostly higher educated. Of the patients, 63% presented with unexplained fatigue. On average, quality of life was remarkably poor (mean
RAND-36 domain scores 37-73), also in comparison with other groups. The chapter concludes that future research should explore how early identification of patients at risk of developing chronicity can take place and that awareness of potential poor quality of life may influence GPs' medical decision-making.

Chapter 6

Chapter 6 deals with the yield of blood test ordering of restricted and elaborate test sets for patients with unexplained fatigue. We looked into the relationship between established diagnoses and the occurrence of abnormal test results among patients with these complaints, both when tests were ordered immediately at presentation and when they were postponed. Furthermore, we explored whether there are consultation-related determinants that may predict the presence of abnormal blood test results. In this cluster-randomised part of the trial, data of 325 patients with unexplained fatigue were analysed (71% women; mean age 41 years). After follow-up, eight percent of the patients happened to have a somatic illness that theoretically could have been detected by blood test ordering. The number of false positive test results increased in particular upon the expansion of the test set. Patients rarely re-consulted after four weeks. Test postponement did not affect the distribution of patients over two-by-two tables. No independent consultation-related determinants of abnormal test results were found. Our findings support the advice in the DCGP guideline to restrict the number of tests ordered and to postpone blood test ordering in patients with unexplained fatigue in general practice.

Chapter 7

This chapter discusses the trial results that concern the patients' satisfaction with care and anxiety after the consultation in relation to immediate versus postponed blood test ordering. In total, 498 patients and 63 GPs completed questionnaires about demographic characteristics, satisfaction with care, anxiety and aspects of the consultation, e.g. signs, symptoms and communication. In addition, laboratory test result forms were collected. The mean levels of satisfaction with and anxiety after the consultation (on a 10-point scale) were 7.3 and 3.1 respectively. These figures did not differ significantly between the 3 study groups (immediate blood test ordering, postponed blood test ordering and postponed blood test ordering combined with a quality improvement strategy for the GPs). Factors influencing satisfaction and anxiety were mainly related to physician-patient communication, rather than the blood test ordering approach. Apparently, GPs underestimate how much they can contribute to the well being of their patients by discussing their worries.
Chapter 8

The transition of newly presented to persistent unexplained complaints and its risk factors are scarcely investigated. Our objectives in this chapter were to study to which diagnoses newly presented unexplained complaints lead, which proportion of newly presented unexplained complaints persists and to identify their determinants. Furthermore, we studied determinants of quality of life over time. We addressed our study population as a prospective cohort. Data came from case record forms, patient questionnaires and electronic medical registrations at inclusion and 1, 6, and 12 months later. Our 63 GPs included 444 analysable patients (73% female; mean age 43), predominantly with unexplained fatigue. We found that 43% was still or once again suffering from these complaints 12 months after initial presentation. Overall, almost 60% of the newly presented unexplained complaints remained unexplained over time. Persistently unexplained complaints followed a varying pattern of presence and absence over time. Among the 40% complaints explained after follow up, both psychosocial (depression, surmenage) and somatic diagnoses (infections/inflammations and arthrosis/degenerative abnormalities) were frequently established. Longer duration of the complaint before presentation was associated with lower probability of its resolution. Patients with new UCs tend to have a poor quality of life and we did not find strong determinants that influence this tendency. Especially having musculoskeletal complaints and having had previous episodes of the same complaint were associated with a worse course of quality of life on the physical dimension. The longitudinal course of the mental summary scale of quality of life was predominantly negatively influenced by having fatigue, having had previous episodes of the same complaints and the presence of psychosocial factors. In our opinion, our findings should stimulate GPs to take UCs more seriously as from their initial presentation. Paying attention to the determinants we found may be helpful in the early detection of patients with an unfavourable course of complaints and quality of life in patients with newly presented UCs in general practice.

Chapter 9

As an example of how to evaluate new blood tests before use in daily practice, the diagnostic accuracy of carbohydrate deficient transferrin (CDT) was systematically reviewed. Excessive alcohol consumption can be one of the (hidden) causes of unexplained complaints. This relatively new blood test was supposed to have better properties for detecting excessive alcohol consumption than for example mean corpuscular volume (MCV) and gamma glutamyl transferase (GGT). We found that the sensitivity of CDTect (14 data points) ranged from 20 to 85%, whereas its specificity ranged from 77 to 95%. The sensitivity of CDTriTIA (4 data points) ranged from 10 to 67%, and its specificity
ranged from 90 to 100%. The heterogeneity of results could not be explained clinically. The chapter concludes that the validity of CDT as a diagnostic tool is still questionable. If, in future, the higher values for sensitivity that some studies report, could be confirmed by others, it might be a useful diagnostic tool in unselected populations. However, more methodologically sound, comparable studies needed to be performed before firm conclusions can be drawn.

Chapter 10
The general discussion starts by exposing the unequivocal concepts and definitions of unexplained complaints. Subsequently, the main findings of the study per chapter are discussed in a broader context. Further on, the general topic of insufficient GP and patient recruitment is elaborated upon. Finally, implications of the studies for daily practice are discussed. For daily general practice, the implications relate particularly to doctor-patient communication. Future research should focus on the development of early interventions to prevent evolution into established unexplained complaints.