SUMMARY AND CONCLUSIONS
The first part of this thesis included three studies on clinical and patient reported outcomes in the treatment of vitiligo. In the second part, the focus was on health-related quality of life (HRQL) and other patient reported outcomes in vitiligo.

The general introduction in **Chapter 1** provided a brief overview of the aetiology, pathogenesis and current treatment options for vitiligo as well as of clinical and patient reported outcomes used in vitiligo research.

In the absence of a consensus on well-defined, quantitative, outcome measures, it is difficult to pool and to compare the results of clinical studies in vitiligo. Therefore, in **Chapter 2**, a systematic review was presented on the properties of clinician, patient and observer reported outcomes measures. These properties were summarized and critically appraised. Electronic databases MEDLINE, EMBASE and CINAHL were searched. The COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN), an instrument to evaluate the methodological quality of studies on measurement properties was used to calculate the overall level of evidence per measurement property of each instrument. Fourteen studies involving 11 measurement instruments met the inclusion criteria. It appeared that recommendations on the use of specific outcome measures for vitiligo should be formulated with caution: current evidence is insufficient due to the low number of studies, their relatively poor methodological quality, and unclear clinical relevance. Strong evidence was found for a good internal consistency of the quality of life questionnaire Dermatology Life Quality Index (DLQI). For other instruments the evidence of measurement properties was limited or unknown. In order to be able to recommend on outcome measures for vitiligo, further research on measurement properties of clinically relevant outcome measures for vitiligo according to COSMIN quality criteria is needed.

In **Chapter 3** repigmentation of vitiligo lesions after punch grafting was assessed in three ways, and the results of these assessments were compared with each other. In 21 patients, one specific vitiligo patch was selected. This patch was treated with the punch grafting technique. The grade of repigmentation (%) after 3 months was assessed by i) a digital image analysis system (DIAS), ii) 3 clinical observers and iii) patients themselves scoring the grade of repigmentation by photographs of the lesions. Physicians and patients also evaluated the global result on a 7-point scale. The scores of DIAS, clinical and patients’ assessment were compared and correlations were calculated with the use of the intra-class correlation (ICC) coefficient. ICC values of 0.80–1.0, 0.60–0.80, and 0.40–0.60 are generally considered to indicate “almost perfect,” “substantial,” or “moderate” agreement, respectively. We found an almost perfect agreement between the three clinical observers and the DIAS (ICC 0.83). However, there was a large variation between the three clinical observers which is not uncommon in visual assessment. Patients’ scores showed a moderate agreement with the DIAS (ICC 0.49) and a poor agreement with the physicians (ICC 0.28). Overall, the patients were more satisfied with the results than the physicians.
The DIAS can overcome the inevitable differences between observers, such as inter-rater and intra-rater variability, inherent in visual grading. Therefore, it appeared to be a good objective tool for the assessment of repigmentation in vitiligo patches, thereby enabling reliable cross-treatment and cross-study comparisons. However, this technique is complex and laborious. Therefore, it was suggested that the DIAS should be used in clinical trials in which only a small number of lesions needs to be evaluated.

Phototherapy following punch grafting may stimulate the migration of melanocytes from the grafts into the vitiliginous skin, thereby increasing the rate of repigmentation. In Chapter 4 we described a prospective, single blinded, randomized within-patient controlled study comparing the effects of phototherapy using the 308-nm xenon chloride excimer laser (EL) versus Narrow Band UVB (NB-UVB) treatment after punch grafting in vitiligo patients. Fourteen patients were treated with the punch grafting technique on two symmetrical vitiligo patches. Starting 1 week after the punch grafting, the vitiligo patches were treated twice a week during 3 months, with EL on one side and with NB-UVB on the other side. Repigmentation (%) was measured by a DIAS. Patients’ satisfaction with- and preference for treatment were also assessed.

Contrary to our expectations, EL did not result in a higher degree of repigmentation as compared to NB-UVB; results were comparable. However, with EL, a 71.4% lower cumulative dose was reached compared to NB-UVB. Interestingly, patients favoured the NB-UVB treatment as they were more satisfied with it and preferred it over EL. The choice between EL and NB-UVB cannot solely be based on repigmentation, but rather on other factors, such as patients’ preferences. Given the lower UV dose of EL, we recommend its use in selected patient groups, such as small children and patients with sun-damaged skin and/or a history of long-term UVB treatment.

In Western societies, vitiligo is often regarded as a harmless cosmetic skin problem. As a consequence, the relevance of treating vitiligo patients is often underestimated. In Chapter 5 we described a study estimating the burden of vitiligo in a large cohort of vitiligo patients by measuring their health-related quality of life (HRQL) with two questionnaires; the generic, 36-item Short-Form General Health Survey (SF-36) and the dermatology-specific questionnaire, the Skindex-29. The SF-36 is a widely used questionnaire. It consists of 36 items forming eight domains or scales. Two summary scores were calculated; the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The Skindex-29 consists of 29 items forming three scales (symptoms, emotions and functioning).

All consecutive adult patients (age ≥18 years) with generalized vitiligo, referred to the Netherlands Institute of Pigment Disorders (NIPD) from January to December 2006, were invited to participate in the study. A total of 245 adult patients with generalized vitiligo (response rate=98.8%) completed the two quality of life questionnaires. Physicians assessed sociodemographic and clinical
characteristics of these patients. A descriptive analysis was carried out to assess the characteristics of the sample.

Our results indicated that adult patients with generalized vitiligo have a MCS score lower than that of the general population and comparable to that of patients with other skin diseases, such as atopic eczema, psoriasis and hand eczema. Measurement with the dermatology-specific Skindex-29 revealed that in patients with generalized vitiligo, scores on the emotions scale were higher (which means more problems in emotional life) than scores on the symptoms and functioning scale. Scores on the emotions scale were also comparable to that of patients with psoriasis, atopic eczema, chronic hand dermatitis and acne. Moreover, vitiligo appeared to be associated with itch in 20% of the patients. Unexpectedly, localization of vitiligo on visible areas, like hands and face, did not appear to be a major determinant for loss of HRQL, whereas localization on the chest, especially in women, was associated with lower HRQL. Furthermore, and not unexpectedly, generalized vitiligo particularly affected patients with a dark skin (skin type IV-VI). In fact, skin type was the only clinical patient characteristic that was independently associated with both generic and dermatology-specific loss of HRQL. Further longitudinal studies are needed to obtain additional insight into the stability of the associations found in this study, and in order to evaluate the efficacy of medical and/or psychological interventions in patients with an impaired HRQL.

In Chapter 6 a retrospective cohort study focusing on patient characteristics and HRQL of patients with universal vitiligo was presented. The characteristics and the HRQL of 55 patients with universal vitiligo were compared with those of 110 patients with generalized vitiligo.

Patients with universal vitiligo reported a higher percentage of affected family members compared to patients with generalized vitiligo (47% versus 35%). Moreover, patients with universal vitiligo reported significantly more comorbidity like rheumatoid arthritis (15%) and alopecia areata (7%) than patients with generalized vitiligo (3% and 0% respectively). Surprisingly, the impact on HRQL was comparable to what was found in generalized vitiligo except for poorer functioning in daily life and physical HRQL, which possibly reflects the difference in comorbidity as described above.

In half of the patients, vitiligo starts before the age of 20 years. Having a chronic disease in childhood could impede a child’s well-being and development. In Chapter 7, data on developmental milestones, negative experiences during childhood and HRQL in young adult patients suffering from vitiligo since childhood, were compared to data from healthy controls. Furthermore, outcomes in patients reporting disease-related negative childhood experiences were compared with those from patients not reporting negative childhood experiences.

Eligible patients were mailed questionnaires on (i) sociodemographic and clinical characteristics, (ii) social and psychosexual development (two scales of the Course of Life questionnaire), (iii) generic (SF-36) and dermatology-specific
(Skindex-29) HRQL, (iv) presence of negative childhood experiences related to vitiligo, (v) specification of these negative experiences, and (vi) patients’ recommendations for further care.

A total of 232 patients with vitiligo completed the questionnaires. We found that the social and psychosexual development during childhood and current generic HRQL in young adult patients in whom vitiligo was diagnosed in early childhood were not different from a group of healthy controls. However, patients reporting negative vitiligo-related experiences during childhood reported significantly more problems in social but not in psychosexual development. The most important finding of this study was that the report of negative vitiligo-related experiences in childhood appeared to be significantly associated with HRQL impairment in young adults with vitiligo. We suggest that young adults with vitiligo should be screened for HRQL impairment by the following simple question: “Did you have negative experiences from vitiligo in daily life during childhood?” We recommend physicians to provide more guidance to their vitiligo patients, especially those who report negative experiences.