The main objective of this thesis was to assess the feasibility, effectiveness and cost-effectiveness of integrated care for patients with moderate to severe chronic hand eczema. Therefore, we performed a randomized controlled trial to compare integrated care with usual care, the HAND study. The first chapters of this thesis describe three sub-objectives. First, to systematically summarize the literature on the effectiveness of prevention and treatment options for patients with hand eczema. Second, to describe the design of the HAND study. The remaining chapters describe the feasibility, short and long term effectiveness and the cost-effectiveness of integrated care compared to usual care.

This chapter starts with a summary of the main findings of this study. These findings will be compared to results described in existing literature. Furthermore, methodological aspects of this study will be discussed. In the final part of this chapter, implications of the study results for future research and practice will be discussed.

**The main findings from this thesis**

We showed in a systematic review that there is moderate evidence for the effectiveness of secondary prevention programs for individuals with hand eczema on reducing prevalence of self reported hand eczema and improving adherence to preventive measures. It was also shown that there is low evidence for the effect on improving clinical outcomes of hand eczema patients. No studies were found measuring the cost-effectiveness of primary and/or secondary prevention for patients with hand eczema. An integrated care program was developed and evaluated in a randomised controlled trial. The clinical score HECSI was used as the primary outcome measure in this study. Integrated care proved to be effective after 26 weeks of follow-up in patients with moderate to severe hand eczema. Patients in the integrated care group improved significantly more on HECSI score compared to patients in the usual care group. However, the difference in improvement on HECSI score between the integrated care group and the usual care group was no longer significant after 52 weeks.

The economic evaluation, carried out from a societal perspective, showed that integrated care was borderline cost effective compared with usual care. Of all pairs of costs and effects, 93.8% indicated that integrated care was more effective, but also more expensive, compared to usual care after 52 weeks. No significant differences in improvement on any secondary outcome measures have been found after both 26 and 52 weeks.

A process evaluation showed high satisfaction with the integrated care program of patients as well as the health care professionals involved in the program. Health care professionals evaluated the multidisciplinary character and the direct lines of communication within the multidisciplinary team as the most positive aspects of integrated care. The process of care can be improved though. The most perceived barriers for implementation by the health care professionals were the lack of flexibility of the protocol, the expected high costs of the
intervention and a lack of specific knowledge on hand eczema available in other hospitals. Overall conclusion: integrated care has shown to be a useful and effective treatment for patients with chronic hand eczema on the short term, and we hypothesize that the program may be (cost)-effective on the long term if adaptations in the integrated care program are implemented.

Conceptual model

In the development of the integrated care program, we used the International Classification of Functioning, Disability and Health (ICF) as conceptual model[1]. Figure 1 shows our conceptual model, based on the ICF.

To improve participation in hand eczema patients, not only symptoms, but also personal and external factors should be taken into account. Figure 1 shows how the integrated care program targets these personal and external factors by using a biopsychosocial approach, consisting of three major components: a biomedical, psychological and social component. First, the biomedical component and medical factors associated with hand eczema at work were addressed by targeting external factors. Topical treatment was standardized and strictly protocolled. Based on the status and severity of the hand eczema, a topical treatment regimen was selected and adjusted throughout the intervention if needed[2,3]. According to figure 1, we expected a positive effect on clinical outcomes and thus on HECSI score as a result of topical treatment and skin care.

Second, the psychological component and mediating personal factors associated with hand eczema at work were addressed. Personal factors such as coping and compliance were taken into account by giving instructions on self-management and the use of preventive measures [4,5]. We expected the repeated embedding of instructions on self-management during multiple consultations to increase the compliance to topical treatment as well as to the use of preventive measures[4,6]. Coping with hand eczema was addressed by means of counselling, which we expected to provide an improvement in activities and participation, and thus in quality of life[7] (see figure 1).

Third, the sociological component and mediating environmental factors associated with hand eczema at work was targeted by involving external factors at the workplace. We expected the avoidance of relevant contact factors and provision of work adaptations to have a positive effect on environmental factors and on participation[8-10]. Specific advises about prevention and work procedures and communication with the work place should lead to a decrease in absenteeism and an increase in work performance[11]. In addition, the environmental component of integrated care consisted of the multidisciplinary team discussion of each patient to avoid conflicting advises of health care professionals.

In all three components of the treatment, personal as well as environmental factors were
taken into account, since they have a major effect on activities and participation (see figure 1). Since the last 2 out of 3 three components are putatively less addressed in usual care, we expected integrated care to be more effective and cost-effective on both clinical outcomes (HECSI) and quality of life (Skindex) than usual care.

Figure 1. Conceptual model for integrated care for hand eczema, based on the ICF and biopsychosocial model.
Interpretation of the results

Integrated care was significantly more effective on improvement of HECSI scores than usual care after 26 weeks of follow-up. After 52 weeks, integrated care turned out to be more expensive but was still more effective, although no longer statistically significant. No effects were found for integrated care on quality of life compared to usual care after 26 and 52 weeks.

The lack of (cost)-effectiveness after 52 weeks may be a result of shortcomings in the design of the study. First, the inclusion criteria were rather broad. This resulted in a low average HECSI score at baseline, which left little room for (a difference in) improvement due to ceiling effects. Also, the low average baseline HECSI in combination with a fast short-term improvement as a result of topical treatment may have had an impact on the effects of the counselling. When patients perceived a fast improvement of their hand eczema, they may have been less inclined to comply to the advises and counselling from the specialized nurse, resulting in less improvement in quality of life than expected from the conceptual model.

Second, since a relation with work was not an inclusion criterion, only a relatively small number of participants suffered from work-related hand eczema. Only 29% of patients in the intervention group had an indication to visit the clinical occupational physician. In addition, the process evaluation showed that the clinical occupational physician was consulted only in 62% of the indicated patients. Our hypothesis was that patients with work-related hand eczema would profit the most from integrated care based on the unique social component in integrated care. The minimal involvement of the clinical occupational physician in the treatment implies, according to the conceptual model, that minor attention has been addressed to environmental factors and may thus have led to less positive results than expected.

Finally, the integrated care program may have been suboptimal. Our process evaluation showed that some of the health care professionals perceived the protocol as not flexible, and suggested that the intervention period could be stretched for indicated patients over a longer timeframe. Application of the suggestions made by the health care professionals may result in an extension of the effect of integrated care.
Comparison with other studies

Studies have investigated intervention programs that are partly comparable to our integrated care program in patients with hand eczema[8-10]. One study investigated a comparable program in a different population, i.e. patients with chronic low back pain on sick leave[12,13]. To our knowledge, no research has been done with an identical intervention for patients with moderate to severe chronic hand eczema.

The study on integrated care for patients with low back pain was carried out by Lambeek et al[12,13]. In this study, occupational care and clinical care were integrated and care was coordinated by a clinical occupational physician. They found that integrated care was effective and cost-effective for patients with chronic low back pain on the primary outcome measure, i.e. cumulative days until return to work. Participants needed to be on sick leave to take part in the study. Since this was not an inclusion criterion in the current study, the clinical occupational physician was not actively involved in the treatment of all participants in the integrated care group. However, the study of Lambeek and colleagues showed that integrated care can be effective, at least in patients with low back pain.

Although most studies conducted in the field of hand eczema comprised topical treatment only, some research has been carried out also evaluating the effectiveness of prevention programmes and/or preventive measures. Those studies have been systematically reviewed in chapter 2 of this thesis. The main difference between the current study and the studies included in the systematic review is that in the current study all patients suffered from hand eczema independent of their profession, whereas in the studies reviewed the study population existed of patients with hand eczema in a well-defined profession. Despite this difference, the current study meets the inclusion criteria we used in the systematic review. When adding the results of the current study to the systematic review, the first step to be taken is to determine the risk of bias using the same quality assessment list that was used in our systematic review. In our systematic review, a study was considered as ‘low risk of bias’ when at least 50% of the 12 criteria defined previously were met, otherwise the study was considered as ‘high risk of bias’ (Table 1).

Two reviewers (RG and PG) independently assessed the risk of bias of our RCT. Table 1 presents the risk of bias assessment score. The current RCT would receive 9 out of 11 points, indicating a low risk of bias.

The short term results of our study can be added to our systematic review towards the effects on clinical outcomes and skin condition and towards the effects on self-reported outcomes. The level of evidence of effects on clinical outcomes would increase from low to moderate, since studies’ limitations is not a factor anymore. The same argument counts for the effects on self-reported outcomes, which also increases from low to moderate level of evidence.
Table 1. Quality assessment of the RCT from the HAND study

<table>
<thead>
<tr>
<th>Component</th>
<th>Judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Randomization procedure</td>
<td>+</td>
</tr>
<tr>
<td>2. Concealed treatment allocation</td>
<td>+</td>
</tr>
<tr>
<td>3. Blinding of patient</td>
<td>-</td>
</tr>
<tr>
<td>4. Blinding of care provider</td>
<td>NA</td>
</tr>
<tr>
<td>5. Blinding of outcome assessor</td>
<td>+</td>
</tr>
<tr>
<td>6. Drop-out rate</td>
<td>+</td>
</tr>
<tr>
<td>7. Intention-to-treat analysis</td>
<td>+</td>
</tr>
<tr>
<td>8. Free of suggestion of selective outcome reporting</td>
<td>+</td>
</tr>
<tr>
<td>9. Baseline characteristics</td>
<td>+</td>
</tr>
<tr>
<td>10. Co-interventions</td>
<td>?</td>
</tr>
<tr>
<td>11. Compliance</td>
<td>+</td>
</tr>
<tr>
<td>12. Outcome assessment</td>
<td>+</td>
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</table>

**Strengths and weaknesses**

**Quality of the study**

As mentioned above, the randomised controlled trial of the HAND study meets the criteria for low risk of bias, indicating that the HAND study is of high quality. However, the loss to follow-up rates were not acceptable for the cost data (only 67.1% of all cost data were completed). High loss to follow-up rates may have introduced selection bias[14]. To investigate the presence of selection bias, we checked our data for selective drop-out. Non-response analyses showed no differences on several prognostic factors (age, gender, risk profession, baseline HECSI, history of atopic eczema) between participants who completed the study and those who had dropped out. Therefore, we conclude that it is unlikely that our findings in the economic evaluation were influenced by the considerable loss to follow-up rates.

**Study population**

The selection of patients was time consuming. The inclusion period lasted one year and 6 months in which patients were recruited from five participating hospitals. Taking into account 30 dropouts (15%), 200 patients had to be included during this period according to the sample size calculations. This number turned out to be challenging during the first months of inclusion. A few weeks into the inclusion period, the decision was made to expand the initial inclusion criteria (moderate to severe, chronic hand eczema according to the photographic guide[15], >16 years old), adding the criterion that patients with mild
hand eczema who were on sick leave from work, or who scored at least 4 points on a Visual Analogue Scale (VAS) for perceived burden of disease in the last three months before inclusion were also eligible to participate. Our reasoning was that due to the dynamic course of hand eczema, baseline severity was not always a good measure for the perceived burden of disease. This may have caused a decrease in the average HECSI score at baseline in both groups and may have resulted in an underestimation of the effect since the margin for the integrated care group to improve may have decreased. This hypothesis is confirmed by a subgroup analysis where the study population was divided by the median HECSI at baseline (not presented in this thesis). This subgroup analysis shows a positive effect of integrated care compared to usual care for patients with a high HECSI at baseline. However, this effect is not significant due to a lack of power (p=0.13).

The primary outcome: HECSI
The clinical score HECSI is often used in general practice and has a good inter-observer reliability[16], which is important since scoring in different hospitals was performed by different observers.

Loss to follow-up
The loss to follow-up in this study can be considered high. Regarding the primary outcome, 28 of the 196 initial participants (14%) were lost to follow up for the primary outcome measure, which is reasonable. This number was slightly higher for the secondary outcomes. However, regarding the cost effectiveness, loss to follow up was up to 32.9% of all cost data and/or data on sick leave. This may have influenced the validity of the results of the economic evaluation, since a lot of data had to be imputed. By far the largest portion of missing cost data comprised of cost-calendars not being returned. This may have to do with the monthly posting of the calendars: it is more difficult to keep track for the researchers and it is likely that a patient is more prone to fail to complete 12 monthly calendars than for example four calendars measuring a three month period. Disadvantage of the latter option is that recall bias might be induced. Missing data on both the effect and the cost side were evenly distributed over the integrated care group and the usual care group.

Cost categories
An underestimation of the costs of productivity loss is likely since costs of presenteeism, loss of productivity caused by reduced productivity when an employee is at work, were not considered. According to a review of Schultz et al.[17], 70% of all costs in allergies including hand eczema can be attributed to presenteeism. In our study, we found more positive results for work performance in the intervention group compared to the control group.
Since work performance can be used as a proxy for presenteeism, we expect that inclusion of presenteeism costs would increase indirect costs in the usual care group more than in the intervention group. This means that the cost-effectiveness of integrated care may have been underestimated by not including presenteeism cost in this study.

**Programme failure or theory failure?**

The lack of effects in the long term and of cost-effectiveness can be caused by both programme failure and theory failure. Programme failure implicates that no results were found due to poor implementation of an intervention.

Several aspects may indicate that the lack of results on the long term is due to the presence of programme failure. First, integrated care for hand eczema may have failed because the intervention protocol was not properly followed. As we describe in chapter 4 (process evaluation), many patients who were in a risk profession were not directed to the clinical occupational physician, and only 62% of the patients with an indication did visit the COP. Second, the protocol might have been implemented differently in one hospital. In Nijmegen, only two patients out of 85 had an indication to visit the clinical occupation physician, compared to 13/64 and 14/47 in Amsterdam and Groningen respectively. Although the latter two hospitals are traditionally more known for their experience with patients with work-related hand eczema, the discrepancy is obvious.

Third, the relation between contact factors in work and other activities and the severity of hand eczema in the population may have been lower than expected, which resulted in less effect of the intervention program. This is the result of the broad inclusion criteria used in this study, which made the inclusion of non-contact eczema possible. Subgroup analyses showed that the groups with high HECSI baseline scores and/or work-related hand eczema improved more than groups with lower baseline HECSI and/or no relation with work.

Last, patients in the control group improved a lot during the follow-up period, which was unexpected. In patients with more therapy-resistant eczema the programme might have been more effective as compared to usual care.

Theory failure implicates that the underlying theory of the intervention was not correct. Even with perfect implementation, the intervention would not lead to improvements on the outcome measures. This is not the case in this study. Although only on the short term, integrated care has proved to be effective for patients with hand eczema. Subgroup analyses support our hypothesis that patients with work-related and/or more severe hand eczema favour the most from integrated care. Thus, there is no indication that the results from our study were affected by theory failure.

Based on the above, we can conclude that the lack of an effect in this study after 52 weeks is the result of programme failure. The next paragraph will discuss points for improvement for future studies and practice.
Implications for practice
The results of our RCT showed that integrated care was effective compared to usual care after 26 weeks, and that the effects had diminished after 52 weeks. Integrated care was close to cost-effective after 52 weeks. Based on our findings, we do not recommend implementation of the program in its current form on a large scale. However, integrated care is a useful treatment on the short term and may be useful with some adaptations such as more flexibility regarding the number and time of visits for more severe cases. For the future, we would like to make a few recommendations.

For the dermatologist: the standardized and protocol-led topical treatment seems to have a positive effect on the short-term, and we recommend the use of such a stepwise approach. The number of patients with work-related hand eczema in our study was relatively low. Therefore, it does not seem useful to form a multidisciplinary team including a clinical occupational physician in each department of dermatology. A solution would be to cluster the care for patients with work-related hand eczema in a few specialized centres.

For the patient: subgroup analysis showed a trend that integrated care was more effective for patients with severe to very severe hand eczema, and for patients whose hand eczema was work-related. We recommend patients who fall into either one or both categories, to visit a hospital with a specialized centre.

For the policymaker: although we did not find integrated care to be cost-effective compared to usual care on the long term, the different components may be useful and should be studied more specifically. We recommend policymakers to be supportive regarding new studies with an adapted design as indicated.

Implications for research
This is the first trial to investigate the cost-effectiveness of an integrated care program for patients with moderate to severe, chronic hand eczema. The findings of our study indicate that integrated care could be a promising treatment. To determine if (components of) integrated care can be effectively implemented in the future, more research is necessary. Future research should include cost-effectiveness evaluations including measurement of presenteeism, since presenteeism constitutes a large part of the costs due to productivity loss[17]. Effectiveness of integrated care should be studied within more specific populations with regard to severity and work relations. According to the health care professionals, a more flexible application of the program and a stretched intervention period could be an improvement of the protocol. Future research should study the effectiveness of such adaptations.
References