Evaluation of Efficacy and Safety of Topical Application of Chinese Herbal Medicine for Atopic Eczema:
A Systematic Review and Protocol for Pilot Randomised Double-Blind Placebo-Controlled Trial

A thesis submitted in fulfilment of the requirements for the degree of

Master of Applied Science (Chinese Medicine)

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(BMed)

Discipline of Chinese Medicine
School of Health Sciences
College of Science, Engineering and Health
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August 2011
Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; and, any editorial work, paid or unpaid, carried out by a third party is acknowledged.

Xuming GU

20 August 2011
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Finally, I want to thank my late parents, I have learnt most of what is essential to be a son, brother, husband, and father from them. I love them forever.
## Acronyms and Abbreviations

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<th>Full Form</th>
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<tr>
<td>AD</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>AAD</td>
<td>American Academy of Dermatology</td>
</tr>
<tr>
<td>AE</td>
<td>Atopic eczema</td>
</tr>
<tr>
<td>CDLQI</td>
<td>Children’s Dermatology Life Quality Index</td>
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<tr>
<td>CHM</td>
<td>Chinese herbal medicine</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CM</td>
<td>Chinese medicine</td>
</tr>
<tr>
<td>DLQI</td>
<td>Dermatology Life Quality Index</td>
</tr>
<tr>
<td>EASI</td>
<td>Eczema Area and Severity Index</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacture Practice</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grades of Recommendation, Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
</tr>
<tr>
<td>IDQOL</td>
<td>Infant’s Dermatology Quality of Life Index</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>ISAAC</td>
<td>International Study of Asthma and Allergies in Childhood</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>MD</td>
<td>Difference in means</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT(s)</td>
<td>Randomised controlled trial(s)</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratios</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>---------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>SASSAD</td>
<td>Six Areas, Six Sign Atopic Dermatitis Severity Score</td>
</tr>
<tr>
<td>SCORAD</td>
<td>Scoring Atopic Dermatitis</td>
</tr>
<tr>
<td>SMD</td>
<td>Standardised mean differences</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TIMs</td>
<td>Topical Immunomodulators</td>
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<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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## Chinese Medicine Terminology

<table>
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<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>Channels</td>
<td>Pathways to circulate energy and blood</td>
</tr>
<tr>
<td>Cold property</td>
<td>One of the herbal properties in theory of Chinese Materia Medica. It summaries an action of the herbs for heat syndromes</td>
</tr>
<tr>
<td>Dampness pathogen</td>
<td>One of the six pathogens in Chinese medicine pathology</td>
</tr>
<tr>
<td>Dampness-heat</td>
<td>Combination of dampness and heat pathogens</td>
</tr>
<tr>
<td>Dryness</td>
<td>One of the six pathogens in Chinese medicine pathology</td>
</tr>
<tr>
<td>Fetal toxin</td>
<td>Heat pathogen from birth</td>
</tr>
<tr>
<td>Fire</td>
<td>One of the six pathogens in Chinese medicine pathology</td>
</tr>
<tr>
<td>Heat pathogen</td>
<td>One of the six pathogens in Chinese medicine pathology</td>
</tr>
<tr>
<td>Lung</td>
<td>One of the five viscera in Chinese medicine physiology</td>
</tr>
<tr>
<td>Milk-tinea</td>
<td>Infantile eczema</td>
</tr>
<tr>
<td>Qi</td>
<td>The refined nutritive substance that flows within the human body as well as to its functional activities</td>
</tr>
<tr>
<td>Release exterior</td>
<td>One of the treatment principles in Chinese formula study</td>
</tr>
<tr>
<td>Spleen</td>
<td>One of the five viscera in Chinese medicine physiology</td>
</tr>
<tr>
<td>Stomach</td>
<td>One of the six bowels in Chinese medicine physiology</td>
</tr>
<tr>
<td>Summer-heat</td>
<td>One of the six pathogens in Chinese medicine pathology</td>
</tr>
<tr>
<td>Wind of the four fossae</td>
<td>Atopic eczema</td>
</tr>
<tr>
<td>Wind pathogen</td>
<td>One of the six pathogens in Chinese medicine pathology</td>
</tr>
<tr>
<td>Yin</td>
<td>One of the concepts in Chinese philosophy, opposites to Yang</td>
</tr>
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Summary

**Background:** Atopic eczema (AE) or infantile eczema is a common inflammatory skin disease, which affects 10-20% of children in industrialised countries. Australia was the 12th highest rank of AE incidence in 55 participating countries. AE is characterised by poorly demarcated redness of the skin and associated surface changes such as scaling, swelling (edema), accentuation of the hair follicles and skin thickening (lichenification) as a result of chronic scratching. There are three common quoted diagnostic criteria for determination of AE for the purpose of research and clinical studies, the Hanifin’s criteria, the U.K. Working Party’s diagnostic criteria and American Academy of Dermatology clinical criteria for AE. In addition, reliable scoring instrument such as Scoring Atopic Dermatitis (SCORAD) is fundamental for clinicians to verify the severity, the course and outcomes of treatment for AE. Certain quality of life (QoL) questionnaires have also been developed and validated for assessment of the personal impact and outcomes of the treatment for AE.

The conventional (western) medicine treatment for AE is not satisfactory. Complementary and alternative medicine including Chinese herbal medicine (CHM) has been increasingly used for AE. There are some promising published evidences on oral administration of CHM for AE. However, the benefit of topical application of CHM for AE is not clear.

**Aims:** a) To review fundamental knowledge of AE in perspectives of both conventional medicine and Chinese medicine (CM), b) To evaluate the effectiveness and safety of topical application of CHM in the management of AE by systematically reviewing current available randomised controlled trials (RCTs), and c) To develop a protocol for pilot randomised double-blind placebo-controlled clinical trial for evaluation of the efficacy and safety of topical application of CHM for AE.
**Methods:** We searched any RCTs with topical application of CHM in electronic databases and journals. Trial-design quality was evaluated and intervention outcome data were extracted and analysed. Meta-analysis was conducted by employing RevMan 5. Development of a protocol for pilot RCT of topical application of CHM for AE was under the guidelines of *Australian Clinical Trial Handbook* issued by the Australian Government, Department of Health and Ageing, Therapeutic Goods Administration in compliance with high ethical standard.

**Results:** Three studies involving a total of 452 participants were selected for analysis after screening 164 potential studies. All three included studies reported significant differences between the treatment group and controlled group and claimed that effects of treatment interventions were superior to control. However, due to the low quality of study design which resulted in low level of evidence strength, these claims require more vigorous scientific proof employing well designed randomised controlled clinical trials. As a result, a protocol for pilot randomised double-blind placebo-controlled clinical trial for evaluation of the efficacy and safety of topical application of CHM for AE was developed.

**Conclusion:** The systematic review in this thesis is the first one conducted in topical application of CHM for AE. Detailed analysis of the three included studies led to the conclusion of low level of evidence strength. Thus, they did not provide convincing evidential support for effectiveness of CHM used topically for AE or infantile eczema. Therefore, there is a need to evaluate the efficacy and safety of topical application of a CHM for AE through a well designed, double-blind controlled-placebo clinical trial.
Chapter 1  Introduction

This chapter describes the general background of atopic eczema. It also outlines the aims of the study and organisation of this thesis.

1.1  Background

Atopic eczema (AE) or infantile eczema is a common skin condition which is characterised by poorly demarcated redness of the skin and associated surface changes such as scaling, swelling (edema), accentuation of the hair follicles, and skin thickening (lichenification) as a result of chronic scratching. The stigma of a visible skin disease can affect a person's self-esteem and severe disease is associated with a poor quality of life (QoL) (Schmid-Ott, Burchard, Niederauer, Lamprecht, & Kunsebeck, 2003).

Current treatment for AE has limitations. Topical administration of corticosteroids, as one of the standard first-line therapies for the management of inflammatory episodes of AE, can be associated with certain adverse events such as skin thinning. Long-term application of steroids has been a great concern to those using them and to healthcare professionals (J.M. Hanifin, Cooper, & Ho, 2004). A study showed up to 72.5% of patients or their guardians were concerned about the application of corticosteroids which could lead to potential side-effects for their treatment of AE (C.R. Charman, Morris, & Williams, 2000). New drugs for the treatment of AE such as tacrolimus and pimecrolimus [these two drugs are categorised as topical immunomodulators (TIMs) or calcineurin inhibitors] (Eichenfield, et al., 2002) have been developed as second-line therapies. However, issues regarding the long-term safety of these new drugs, particularly the potential link between TIMs and cancer have been raised (Centre for Drug Evaluation and Research, 2005). Therefore, many AE
sufferers have chosen to use complementary and alternative medicine including Chinese herbal medicine (CHM) for the management of AE (K. L. Hon, Ma, Wong, Leung, & Fok, 2005).

In Chinese medicine (CM), those with AE are recognised as having a specific constitution that leads to internal dampness-heat accumulated due to the reduced function of the Spleen. Symptoms can be triggered by exposure to wind, dampness, and heat pathogens (B. N. Zhao & Zhang, 1983). Clinically, AE is classified into the following patterns from a CM viewpoint: Accumulation of internal dampness, Excess of dampness with Spleen deficiency, or Yin deficiency with dryness of blood (G. T. Chen & Yang, 1991). CHM is one of the important components in CM for prevention and treatment of diseases. Botanical resources such as barks, seeds, flowers, roots or mineral substances are prescribed and administered in forms of decoctions, pills, washing lotions, or ointments for conditions diagnosed by a CM practitioner. CHM has been employed for the treatment of AE for many years. Chinese herbs for AE may be administered orally and/or topically (D. C. Chen & Xuan, 2001). The formulation of CHM for oral applications is guided by CM pattern differentiation method (Bian Zheng 表证) known as "individualised treatment" while topical administrations have been devised with little or no consideration of pattern differentiation (Guo & Yu, 2007; Zhou & Li, 2008). Efficacy of oral administration of CHM for AE has been assessed through clinical trials (K. Hon, et al., 2007; Zhang, et al., 2004). However, topical application of CHM for AE has not been properly evaluated in terms of efficacy and safety. Given the wide use of CHM in AE sufferers, it is important to systematically evaluate the therapeutic effects and safety of CHM used topically for management of AE.
1.2 Aims of this Study

The aims of this study are to (1) review fundamental knowledge of AE from both perspectives of conventional (western) medicine and Chinese medicine, (2) investigate the effectiveness and safety of topical application of CHM for AE by systematically reviewing the currently available randomised controlled trials (RCTs), and (3) develop a protocol for conducting a pilot randomised, double-blind, placebo-controlled clinical trial for the management of AE with topical application of CHM.

1.3 Organisation of the Thesis

The thesis consists of six chapters. The current Chapter One provides a general introduction to the background, aims of the study and organisation of the thesis. Chapter Two reviews the definition, aetiology, pathogenesis, diagnosis and treatment of AE from conventional (western) medicine and Chinese medicine perspectives. Chapter Three describes the detailed methods used for the systematic review and outlines the methodology for development of a protocol for RCT. Chapter Four reports the findings of the systematic review, including details of the study selection process, characteristics of included studies, and effects of CHM by comparing them with no treatment, placebo or conventional medications. The significance and limitations of this study are discussed in this chapter as well. Chapter Five describes the development of a protocol for pilot RCT in management of AE with CHM in topical administration. Chapter Six is the final chapter in which the general discussion and conclusion are presented.
Chapter 2  Literature Review

This chapter reviews fundamental knowledge of AE from the perspectives of conventional/western medicine and Chinese medicine.

Section I: Conventional / Western Medicine Perspective

2.1 Definition of AE

The term eczema applies to inflammatory skin disorders caused by either exogenous or endogenous factors or both. The exogenous group of eczema includes primary irritant eczema, contact allergic eczema, and infective eczema secondary to pathogens. Endogenous group includes atopic eczema, seborrhoeic eczema, discoid eczema, pompholyx eczema (hand and foot eczema), static eczema (venous eczema), asthetotic eczema, xanthoerythrodermia perstans (superficial scaly dermatosis), lichen striatus, photo-provoked eczema, and neurodermatitis (Graham-Brom & Bourke, 2007). Among the endogenous group of eczema, atopic eczema is a common inflammatory superficial skin disease characterised by severe pruritus and associated with a personal or family history of related atopic disorders such as asthma or allergic rhinitis (Beers & Berkow, 1999). As eczema and dermatitis are synonymous (Graham-Brown & Burns, 2002), the abbreviation of AE or AD is interchangeable for atopic eczema and atopic dermatitis in this study. In addition, as there is a consensus that infants or children under 16 years old who were diagnosed with “eczema” are also considered as AE in this age group (Simpson & Hanifin, 2006) and AE usually starts during the infancy (Carbone, Siu, & Patel, 2010); therefore, infantile eczema or childhood eczema is regarded as equivalent to AE in this thesis.
2.2 Epidemiology of AE

Industrialised countries have reported a higher incidence of AE with around 10-20% of children being involved (Kerdel & Jimenez-Acosta, 2003). AE affects population from less than 2% in Iran to over 16% in Japan and Sweden in the six to seven year old children and less than 1% in Albania to over 17% in Nigeria for the 13 to 14 year age range (H. Williams, et al., 1999). Data from the International Study of Asthma and Allergies in Childhood (ISAAC) on symptoms of eczema were published in 2009 (Odhiambo, Williams, Clayton, Robertson, & Asher, 2009). In this study the authors found in six to seven year-old children from 143 centres in 60 countries, disease prevalence ranged from 0.9% in India to 22.5% in Ecuador. Amongst 13 to 14 year-olds from 230 centres in 96 countries, disease prevalence ranges were found from 0.2% in China to 24.6% in Colombia. Although industrialised countries have previously been reported to have a higher disease prevalence (Kerdel & Jimenez-Acosta, 2003; Mohrenschlager, Darsow, Schnopp, & Ring, 2006) data from the ISAAC study suggest that eczema is a big problem in developing countries as well, especially in Latin America and some countries in Africa. Australia was the 12th highest rank of AE incidence in 55 participating countries (Kemp, 1999). The prevalence of AE has increased over the last 10 years in both developed and developing countries, especially in those aged six to seven years (H. Williams, Stewart, Von Mutius, Cookson, & Anderson, 2008) for reasons that are unclear. Most children with eczema improve with time, but around 40% persist into adulthood (H. C. Williams & Wüthrich, 2000).

2.3 Impact of AE

AE is an itchy skin condition which can result in sleep loss for the child and family members. The cost of care for patients with AE ranged from US$364 millions to US$3.8 billion per year (Ellis, et al., 2002; Mancini, Kaulback, & Chamlin, 2008) and
employee disability due to AE and increased sick days occupied for 38\% of the cost burden in the United States (Fowler, et al., 2007; Suh, et al., 2007). It was estimated that the total annual expenditure on AE in the United Kingdom was £465 millions (Herd, Tidman, Prescott, & Hunter, 1996). An Australian family and community had to pay AUD$1,142 per child with mild AE a year or AUD$6,099 per child with severe AE (Kemp, 1999). The author further pointed out that AE should not be considered as a minor skin disease but as a condition with significant personal, social and financial burden both to the family and the community (Kemp, 2003).

A recent published prospective cohort study over 40 years showed that childhood eczema was strongly associated with the incidence and persistence of adult atopic asthma. The implications of this study are that prevention and rigorous treatment of childhood eczema may prevent the persistence and development of asthma (Martin, et al., 2011).

### 2.4 Pathogenesis of AE

The causes of AE are still not fully understood, but probably involve an interaction between genetic factors that determine the integrity of the skin barrier and immune responses, and environmental factors such as humidity, irritation from soaps, microbes such as staphylococcus aureus and allergens such as house dust mite. Most children with AE improve spontaneously by puberty, but around 40\% persist with AE into adult life. As mentioned on Section 2.1, most AE patients have family history of atopic phenomena, such as asthma, allergic rhinitis and AE itself; therefore, genetics are fundamentally important in term of AE pathogenesis. Genome screens of families with AE have shown chromosomal regions that overlap with other skin diseases, and inflammatory and autoimmune diseases. The findings suggest a hypothesis of immune dysfunction in AE resulting in Immunoglobulin E (IgE) sensitisation and a secondary
skin barrier disturbance (Morar, Willis-Owen, Moffatt, & Cookson, 2006). In addition to the genetic susceptibility, the interactions between genetic susceptibility and the environment where the patient lives have been observed. As indicated above, incidence of AE in industrialised countries is higher than that in developing countries where both groups of AE patient exhibit equal genetic susceptibility but elements of the environment in industrialised countries have triggered the development of AE. The roles of epidermal Langerhan’s cells binding IgE, T-lymphocyte activation, T-cell proliferation, epidermal lipids, cyclic nucleotide metabolism in the leukocytes, and staphylococcus aureus infection in AE all have been focused on for explanation of pathogenesis of AE (Graham-Brom & Bourke, 2007). Figure 1 outlines pathogenesis of AE.

Figure 1: Pathogenesis of AE
2.5  **Clinical Features of AE**

A most typical form of AE presents with red and inflamed skin on the face and associated with intense itchiness (Figure 2). As time goes by, the neck, trunk and extensor surfaces of the limbs are affected and finally the flexural surfaces of the extremities such as antecubital and popliteal fossae become involved. Although patients with this condition very often have a dry skin (xerosis), impetiginisation may occur as a result of secondary infection of *staphylococcus aureus* and manifest as weepy and yellow crusts. AE usually presents with the pattern of relapses and remissions, aggravation by intercurrent infection, and teething or allergies. Thickness and roughness of affected skin may be seen in chronic cases (Buxton & Morris-Jones, 2009; Graham-Brom & Bourke, 2007).

Figure 2: Clinical Features of AE

Initial onset of the skin rashes was on three months from new born. She has developed asthma since she turned to 20 months. There were redness and rashes on her face, cheeks and forehead with intense itchiness. The photo was taken by Sherman Gu when the girl was six months old.
2.6 Diagnosis of AE

Distinguishing AE from other forms of eczematous dermatitis is not always easy. There are three common diagnostic guidelines for determination of AE for the purpose of research and clinical studies. They are the Hanifin’s criteria (J. M. Hanifin & Raika, 1980), the U.K. Working Party’s diagnostic criteria (C. Charman, Chambers, & Williams, 2003; H. C. Williams, et al., 1994) and the American Academy of Dermatology (AAD) clinical criteria for AE (Eichenfield, Hanifin, Luger, Stevens, & Pride, 2003).

2.6.1 Hanifin’s Criteria for Diagnosis of AE

Based on their clinical studies and experience, Hanifin and Rajka established the first diagnostic guidelines for AE in 1980. These include major and minor criteria. At least three or more of the following major criteria should be present and plus three or more of the minor criteria in order to diagnose AE.

a) Hanifin’s major criteria for diagnosis of AE

- Skin itching
- Typical dermatitis or eczema which has a history of relapses
- Typical distribution of the skin rashes: facial and outer aspect of arms and legs in infants and children, and lichenous rashes on the flexural areas of the body like elbows, behind knees etc.
- The patient or any of the family members suffering from atopy (allergic diseases) such as asthma, nasal allergy or atopic eczema.

b) Hanifin’s minor criteria for diagnosis of AE
In addition to the major diagnostic criteria above, three or more of the following 15 minor criteria should also be present.

- Dry skin
- Cataract: anterior subcapsular- due to application of steroids near eyes
- Lip dermatitis
- Recurrent eye inflammation and irritation
- Face: pale, red
- Food intolerance
- Hand eczema
- Elevated IgE levels
- Immediate type 1 skin test reactivity
- Recurrent infections
- Itching on sweating
- Pityriasis alba
- White patches on the face and exposed area, showing mild scaling
- White dermographism: on stroking, skin becomes white and raised, instead of red line as in normal people
- Keratinous: cone shaped cornea seen between 20-40 years of age in very severe cases of atopic eczema. Others like Keratosis pilaris (hair follicle oriented hard bumps), nipple dermatitis, dark eye circles, wool intolerance, linear marks on the palms etc.
2.6.2 U. K. Working Party Diagnostic Criteria for AE

As Hanifin’s diagnostic criteria involve eye’s conditions which have to be assessed by an ophthalmologist or conditions need to be assessed by a specialist, a working group of 13 dermatologists, two family medical practitioners and a paediatrician from the United Kingdom was assembled with the aim of developing a minimum list of reliable discriminators for diagnosis of AE. In order to qualify as a case of AE with the U.K. Working Party’s diagnostic criteria, the person must have an itchy skin condition in the last 12 months plus three or more of the following conditions:

- Onset under the age of two (not used in children under four years old);
- History of flexural involvement
- History of a pruritic skin condition
- Personal history of other atopic disease such as asthma (in children aged under four years old, history of atopic disease in a first degree relative may be included)
- Visible flexural dermatitis.

2.6.3 AAD Clinical Criteria of AE:

AAD Consensus Conference on Atopic Dermatitis was held in 2001 and its report was published in 2003. AE is considered as a syndrome rather than a disease. Its clinical diagnostic criteria are:

a) Essential features (must be present)
   - Pruritus
• Eczema (acute, subacute or chronic) with typical morphology and age-specific pattern
• Chronic or relapsing history.

b) Important features (seen in most cases, adding support to the diagnosis)
• Early age at onset
• Personal and/or family history of atopy and IgE reactivity
• Xerosis.

c) Associated features (these clinical associations help diagnosis of AE but are too non-specific to be used for defining or detecting AE for research or epidemiologic studies)
• Atypical vascular responses
• Keratosis pilaris/hyperlinear palms/ichthyosis
• Ocular/periorbital changes and Perifollicular accentuation /lichenification/prurigo legions.

2.7 Assessment of Severity for AE

Because there is lack of biological and pathological criteria i.e. lack of quantitative parameter, diagnosis of AE essentially relies on its clinical manifestations. In addition to establishment of the diagnosis, a reliable assessment system is fundamental for clinicians to verify the severity, the course and outcomes of treatment for AE. Followings are outlines of published and validated scoring system for evaluation of severity of AE. They have been considered the most commonly used scores and adopted for different clinical trials of AE (C. Charman, et al., 2003).
2.7.1 Scoring Atopic Dermatitis (SCORAD)

SCORAD was published by a task force of 10 European experts in 1993 (Stalder & Taieb, 1993). SCORAD combines the objective (extent and intensity of the lesions) and subjective (daytime pruritus and sleep loss) criteria. The objective part of SCORAD has been validated three years after its publication (Kunz, et al., 1997). On SCORAD sheet, the extent of lesions (item A) is scored by using the “Rule of nine” after drawing the lesions on a proposed evaluation form. The intensity of lesions (item B) is recorded by grading each of the six criteria (erythema, oedema/papulation, oozing/crusts, excoriation, lichenification/prurigo and dryness on uninvolved area) on a scale from zero (absence) to three (severe). Subjective symptoms (item C) are scored by Visual Analogue Scale (VAS) from zero to 10. The maximum objective score is 83 (the sum of $A/5 + 7B/2$) and the subjective score C is 20 with a total 103 of SCORAD (Table 1).
Based on the objective SCORAD (from zero to 83 in which the extent of lesions accounts for 25% and intensity of lesions for about 75% of the total objective scores respectively), the severity of AE can be graded into “mild AE” (< 15 on two baseline measurements at a minimum interval of two weeks), “moderate AE” (between 15 and 40 on two baseline measurements at a minimum interval of two weeks) and “severe AE” (> 40 on two baseline measurements at a minimum interval of two weeks).
2.7.2 Eczema Area and Severity Index (EASI)

As SCORAD is a complex and comprehensive system which is designed for pediatric patients; it is believed not efficient for quick assessment of AE for a busy clinical setting. EASI was designed and validated in 2001 based on modifying general scheme used in Psoriasis Area and Severity Index (J. M. Hanifin, et al., 2001).

In EASI, body is divided into four regions:

- Head and neck (H)
- Upper limbs (UL)
- Trunk (T)
- Lower limbs (LL).

Firstly, the intensity of erythema (E), induration/population (I), excoriation (Ex) and lichenification (L) of a representative area of eczema are assessed as none (0), mild (1), moderate (2) and severe (3) by using a Four-point scale. Half scores are accepted. Secondly, the approximate percentage affected region is calculated respectively. In each region, the area is expressed from zero to six as nil (0), 1-9% (1), 10-29% (2), 30-49% (3), 50-69% (4), 70-89% (5) or 90-100% (6). Thirdly, index of proportionate areas of eight years of age or older were multiplied to the intensity and percentage of the affected area. The index of proportionate areas on head/neck is 0.1 for eight years old above, 0.2 for 0 to seven years old; upper limbs is 0.2 for all age groups; trunk is 0.3 for all age groups and lower limbs is 0.4 for eight years old above, 0.3 for zero to seven years old. Finally, the EASI is the sum of above four regions score.

Calculation formula is as following:

$$EASI = [H (E + I + Ex + L) \times \text{Area} (0 – 6) \times 0.1 \text{ or 0.2 for seven years old below}]$$

$$+ [UL (E + I + Ex + L) \times \text{Area} (0 – 6) \times 0.2]$$

$$+ [T (E + I + Ex + L) \times \text{Area} (0 – 6) \times 0.3]$$
Table 2: Eczema Area and Severity Index
[adapted from (J. M. Hanifin, et al., 2001)]

<table>
<thead>
<tr>
<th>Body region</th>
<th>EASI Score$^{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/Neck (H)</td>
<td>(E+I+Ex+L) x Area x 0.1</td>
</tr>
<tr>
<td>Upper limbs (UL)</td>
<td>(E+I+Ex+L) x Area x 0.2</td>
</tr>
<tr>
<td>Trunk (T)</td>
<td>(E+I+Ex+L) x Area x 0.3</td>
</tr>
<tr>
<td>Lower limbs (LL)</td>
<td>(E+I+Ex+L) x Area x 0.4</td>
</tr>
<tr>
<td>EASI =</td>
<td>Sum of the above 4 body region scores</td>
</tr>
</tbody>
</table>

Note: $^1$ For children aged 0-7 years, proportionate areas were head/neck, 20%; upper limbs, 20%; trunk 30%; and lower limbs, 30%.
$^2$ E=Erythema, I=induration/papulation, Ex=excoriation, L=lichenification.
$^3$ Where area is defined on a 7-point ordinal scale: 0=no eruption; 1 ≤ 10%; 2 ≤ 10-29%; 3 ≤ 30-49%; 4 ≤ 50-69%; 5 ≤ 70-89%; and 6 ≥ 90-100%.

Below is an example of EASI calculation:

A three years old child has an acute flare-up of atopic eczema. The flare-up affects limb flexures, and the child's trunk is also rather pink and dry. Less than 10% of the arms, around 60% of the trunk and between 10 and 29% of the lower limbs are affected.

- The head and neck intensity score is nil, as it is not affected. H is 0
- The eczema in the elbow flexure is moderately red, mildly thickened, moderately scratched but not lichenified: UL (2 + 1 + 2 + 0) x 1 x 0.2. UL is 1
- On the trunk it is mildly red, mildly thickened and not scratched or lichenified: T (1 + 1 + 0 + 0) x 4 x 0.3. T is 2.4
- The eczema behind the knees is severely red, severely thickened, severely scratched and mildly lichenified: LL (3 + 3 + 3 + 1) x 2 x 0.3. LL is 6

Rank of EASI score is from 0 (no disease) to maximum of 72 (maximal disease).

Table 2 summaries calculations for patients with eight years of age and older in EASI.
• Total EASI is $H + UL + T + LL = 9.4$.

2.7.3 Six Area, Six Sign Atopic Dermatitis Severity Score (SASSAD)

SASSAD aims to provide a simple and effective system for recording and monitoring disease activity in AE (Berth-Jones, 1996). The score is obtained by six clinical signs of disease intensity (erythema, exudation, excoriation, dryness, cracking and lichenification). Each on a scale of zero (absent), one (mild), two (moderate) and three (severe) and measured at six defined body regions (arms, hands, legs, feet, trunk, head and neck) with a maximum score of 108. It has been validated by different clinical trials of AE; however, its reliability is in doubt as the score is subject to significant inter-observer variation (C. R. Charman, Venn, & Williams, 2002).

2.8 Assessment of Quality of Life

Besides the scoring systems for measurement of severity of the condition, QoL questionnaires have been created for assessment of clinical outcome and impact on QoL of dermatological conditions such as AE, psoriasis and generalised pruritus. It has been shown these three conditions have a greater impact on QoL than acne, basal cell carcinomas and viral warts based on the scores of Dermatology Life Quality Index (DLQI) (Finlay & Khan, 1994). DLQI has been described in over 500 publications including 30 multinational studies since it has been developed and validated. It is the most frequently used instrument as an endpoint in RCTs in dermatology. The children’s DLQI (CDLQI) was initially validated and used for children with skin disorders in 1995 (M. S. Lewis-Jones & Finlay, 1995). The Infant’s Dermatitis Quality of Life (IDQOL) was validated in 2001 (M. S. Lewis-Jones, Finlay, & Dykes, 2001). A specifically designed questionnaire to measure QoL in adults with AE named as Quality
of Life Index for Atopic Dermatitis (QoLIAD) was established in 2003 (Whalley, et al., 2004). It contains 25 items of the QoL index for AE. The items vary from “worry about the appearance”, “no self-confidence” to “worry about meeting people”. Each item scores from zero to one and maximum score is 25. The higher the score of QoLIAD, the lower the QoL is indicated.

2.9 Treatment for AE

Currently, topical application of emollients for management of mild AE is considered one of the first-line therapies for protection and maintenance of skin barrier. Nevertheless, there is no sufficient evidence to support the recommendations of emollients for treatment of AE (Hoare, Li, Po, & Williams, 2000). For moderate and severe AE, oral or topical administration of corticosteroids is the standard first-line therapy, although these treatments are not always satisfactory. In addition, corticosteroids are associated with certain adverse effects, such as skin thinning if used for too long or in too strong a concentration for sensitive sites such as the face where the skin is naturally thinner and the long-term application of corticosteroids has been a great concern to patients and the healthcare professionals (J.M. Hanifin, et al., 2004).

In the past decade, there have been new prescribed medicines such as tacrolimus and pimecrolimus, montelukast and zafirlukast (leukotriene receptor antagonists) available as second-line therapy (Yanase & David-Bajar, 2001). Other therapies such as wrapping the eczematous lesions with silver-coated textiles (Gauger, Mempel, & Schekatz, 2003), and patient education programs (Schnopp, Groer, & Ring, 2003) have also been introduced for management of AE. However, concerns of long-term safety of the new medicines, a potential link between TIMs and cancer (Centre for Drug Evaluation and Research, 2005), and possible silver absorption still remain.
(Mohrenschlager, et al., 2006). As a result, many AE sufferers also used complementary and alternative medicine approaches including CHM for the management of AE (Lee & Bielory, 2010).

### 2.10 Comments

As there is no specific laboratory test to determine AE, Hanifin’s criteria for diagnosis of AE were the first attempt to define the condition clinically. Some associated conditions listed on Hanifin’s minor criteria such as pityriasis alba, cataract and keratinous cornea need to be assessed by a dermatologist or an ophthalmologist, thus simplified diagnostic criteria were setup in the United Kingdom and the United States. The terms of AE or AD are synonymous, AE is frequently used in the UK and AD is more popular in the USA. Diagnostic criteria of the condition in the U.K. Working Party and ADD cover the essential clinical features of AE for establishment of a diagnosis. However, the U.K. Working Party’s diagnostic criteria do not include the children with age of 12 months or less. For this group of AE sufferers, they are often diagnosed with “infantile eczema” by clinicians. It has been debated whether infantile eczema or childhood eczema and children with AE is the same condition. The word “atopic” simply indicates that AE is very often associated with “atopy”, and separates this condition from other type of eczema such as primary irritant eczema, contact allergic eczema and so on. Owing to the fact that onset of AE is usually in early age (under two years old), exogenous factors sometimes are hardly identified for the relapses of the condition, infantile eczema or childhood eczema is often considered as the same condition of children with AE (Simpson & Hanifin, 2006).

For purpose of quantitative analysis and evaluation of severity of AE, scoring systems were developed and validated. These included SCORAD, EASI and SASSAD. SCORAD is one of the most frequent instruments for assessment of severity of AE.
found in published trials. As skin disorders have an impact on the patients’ lives in aspects of psychological well-being, social functioning and daily activities, questionnaires of QoL also have been used for outcome measures in studies of RCTs.

Although there is no evidence to support the benefit of application of emollient for AE, emollient is still being used as one the first-line therapies. AE is not cured with either oral and/or topical administration of steroid. Side-effects of steroid such as thinning of the skin have been the concern for patients and health care providers. TIMs or calcineurin inhibitors are recommended as second-line therapy only if the first-line therapies do not sufficiently control the symptoms and signs of AE, and their safety in long term is still in doubt. Consequently, complementary and alternative medicine including CM is another option for management of AE.
Section II: Chinese Medicine Perspective

2.11 CM Definition and Diagnosis of AE

Although there was no such terminology of AE in ancient CM classical literature, details of “Wind of the four fossae (Si Wan Feng 四弯风) and “Milk-tinea” (Nai Xuan 奶癣) have been recorded. A CM diagnosis of AE or infantile eczema is based on its clinical manifestations and period of eruption of skin rashes. A most typical form of AE presents on face with red and inflamed skin associated with intense itching. As time goes by, the neck, trunk and extensor surfaces of the limbs are affected and finally the flexural surfaces of the extremities such as antecubital and popliteal fossae become involved. Similar descriptions of the symptoms and signs were found on A Comprehensive Summary of Surgery (Wai Ke Da Cheng 《外科大成》) in 1665. It said: “Wind of the four fossae (Si Wan Feng), it shows up on the fossae of the legs and ankles with relapse monthly. It looks like a tinea with intolerant itchiness; it becomes a sore after scratching.” The earliest descriptions of infantile eczema were seen on the Chapter of Pediatric Miscellaneous Diseases, General Treatise on the Causes and Symptoms of Diseases (Zhu Bing Yuan Hou Lun 《诸病源候论》) in year 610. It said: “On the face of a child, it shows squamous and dry skin; it is called milk-tinea.” On a monograph of CM surgery Orthodox Manual of Surgery (Wai Ke Zheng Zong 《外科正宗》) in 1617, it quoted: “Milk-tinea is resulted from parents who are indulgent to spicy and deep fried food. The heat pathogen is then transmitted to the child. Skin lesions are seen on head and face and all over the body surface with discharges, insomnia, restlessness and intolerant itchiness.” On the Chapter of Experimental Therapy in Pomes in Surgery, Golden Rules of Medicine (Yi Zong Jin Jian 《医宗金鉴》), a royal text book of CM in 1739, it noted: “(the skin lesion) appears on vertex of
a child, or on the eyebrows, it is also called milk-tinea. It starts with itchiness and white scales and it looks like tinea...."

Definition of “Wind of the four fossae” (Si Wan Feng) or “Milk-tinea” in CM correlates to AE or infantile eczema in conventional medicine based on the comparison of literature records of CM and the descriptions of clinical features in conventional medicine. Therefore, Si Wan Feng and Milk-tinea in CM were officially defined as AE and infantile eczema respectively in “Criteria of Diagnosis and Therapeutic Effect of Disease and Syndromes in Traditional Chinese Medicine” issued by the State Administration of Traditional Chinese Medicine, China (SATCM, 1994).

2.12 CM Aetiology and Pathogenesis of AE

CHM has been used for treatment of AE or infantile eczema in the form of oral and/or topical administrations for years based on CM aetiology, pathogeneses and diagnosis of AE (D. C. Chen & Xuan, 2001). From a CM point of view, aetiology and pathogeneses of AE or infantile eczema are constitutional insufficiency of the Lung and Spleen. The disease is induced by invasion or transmission of Wind, Dampness and Heat pathogens to the skin. Long standing of relapses and remissions may lead to damage of Yin and body fluids.

Constitutional insufficiency of the qi in Lung and Spleen presents with symptoms and signs of skin dryness and itchiness in AE patient. Skin is dominated by the Lung. Insufficiency of the Lung means that the Lung qi fails to distribute body fluids on the surface of the body which results in dryness and itchiness of the skin. A deficient Spleen slows down its function of transportation and transformation of water and nutrients and leads to deficiency of qi and blood which makes the skin dry and squamous. Parent who was indulgent in spicy and deep-fried food during pregnancy could generate Dampness-heat which could be passed on to the baby to become fetal
toxin (Tai Du 胎毒). Dampness-heat may be transferred to the skin, or there may be contraction of external Wind, or Dampness-heat. They could present with various clinical features of itchiness (Wind predominant), swelling (oedema), weepiness (Dampness predominant), and yellow crusts (Heat predominant). Damage of Yin and body fluids may manifest as skin thickening (lichenification) and dryness of the skin (Xu, 2004). Based on aetiology, pathogenesis and different clinical manifestations of AE, the condition can be subcategorised into three syndromes including Accumulation of interior Damp-heat, Spleen deficiency with excess Dampness, and Yin deficiency with blood dryness. Chinese herbs are prescribed accordingly (G. T. Chen & Yang, 1991).

2.13 CHM Treatment for AE

CHM can be administrated via oral intake or topical application or in combination of both for treatment of AE.

2.13.1 Oral Application of CHMs for AE

a) Accumulation of Interior Damp-heat

i. Clinical features:
Typical AE skin symptoms and signs plus constipations, deep-yellow coloured urine, red tongue and rapid pulse.

ii. Principle of treatment:
Eliminate dampness and clear heat pathogen

iii. Formula:
Modified Expel Wind and Guide Redness Decoction (Xiao Feng Dao Chi Tang 消风导赤汤)

iv. Prescription:
Sheng Di Huang (Radix Rehmanniae Glutinosae) 6g
Jin Yin Hua (Flos Lonicerae) 6g
Bo He (Herba Menthae Haplocalycis) 6g
Huang Lian (Rhizoma Coptidis) 6g
Chuan Mu Tong (Caulis Clematidis Armandii) 4g
Fu Ling (Sclerotium Poriae Cocos) 6g
Bai Xian Pi (Cortex Dictamni Dasycarpi Radicis) 6g
Sheng Gan Cao (Radix Glycyrrhizae) 3g
Deng Xin Cao (Medulla Junci Effusi) 3g

v. Explanation:

Sheng Di Huang (Radix Rehmanniae Glutinosae) cools blood and clears heat. Jin Yin Hua (Flos Lonicerae) and Bo He (Herba Menthae Haplocalycis) release exterior. Huang Lian (Rhizoma Coptidis) dries the dampness and clears interior heat. Chuan Mu Tong (Caulis Clematidis Armandii) eliminates damp-heat by promoting diuresis. Fu Ling (Sclerotium Poriae Cocos) strengthens the Spleen and eliminates dampness. Bai Xian Pi (Cortex Dictamni Dasycarpi Radicis) eliminates dampness and stops itchiness. Sheng Gan Cao (Radix Glycyrrhizae) and Deng Xin Cao (Medulla Junci Effusi) assist Chuan Mu Tong (Caulis Clematidis Armandii) to promote diuresis and guide heat downwards.

b) Spleen Deficiency with Excess Dampness

i. Clinical features:

Typical AE symptoms and signs plus sallow complexion, listlessness, fatigue, poor appetite, loose stools or diarrhea, pale tongue and slippery or soft pulse.

ii. Principle of treatment:
Strengthen the Spleen and eliminate dampness

iii. Formula:

- Child Eliminate Dampness Decoction for Infantile Eczema (Xiao Er Hua Shi Tang 小儿化湿汤)
- Eliminate Dampness in the Stomach with Sclerotium Poriae Cocos Decoction (Chu Shi Wei Ling Tang 除湿胃苓汤)

iv. Prescription:

- Child Eliminate Dampness Decoction for Infants (Xiao Er Hua Shi Tang 小儿化湿汤)
  
  Cang Zhu (Rhizoma Atractylodis) 6g
  Fu Ling (Sclerotium Poriae Cocos) 6g
  Chen Pi (Pericarpium Citri Reticulatae) 6g
  Chao Mai Ya (Fructus Hordei Vulgaris Germinatus, stir-fried) 6g
  Ze Xie (Rhizoma Alsmatis Orientalis) 6g
  Hua Shi (Talcum) 12g
  Sheng Gan Cao (Radix Glycyrrhizae) 2g

- Eliminate Dampness in the Stomach with Sclerotium Poriae Cocos Decoction (Chu Shi Wei Ling Tang 除湿胃苓汤)
  
  Cang Zhu (Rhizoma Atractylodis) 12g
  Hou Pu (Cortes Magnoliae Officinalis) 10g
  Chen Pi (Pericarpium Citri Reticulatae) 8g
  Zhu Ling (Polypours) 12g
  Ze Xie (Rhizoma Alsmatis Orientalis) 12g
  Fu Ling (Sclerotium Poriae Cocos) 12g
  Bai Zhu (Rhizoma Atractylodis) 12g
Hua Shi (Talcum) 12g
Fang Feng (Radix Ledebouriellae Divaricatae) 12g
Chuan Mu Tong (Caulis Clematidis Armandii) 10g
Rou Gui (Cortex Cinnamomi) 3g
Zhi Zi (Fructus Gardeniae) 10g
Deng Xin Cao (Medulla Junci Effusi) 6g
Sheng Gan Cao (Radix Glycyrrhizae) 2g

v. Explanation:

Child Eliminate Dampness Decoction for Infants (Xiao Er Hua Shi Tang 小儿化湿汤)

Cang Zhu (Rhizoma Atractylodis) and Chen Pi (Pericarpium Citri Reticulatae) dry dampness and regulate qi. Fu Ling (Sclerotium Poriae Cocos) strengthens the Spleen and promotes diuresis. Chao Mai Ya (Fructus Hordei Vulgaris Germinatus, stir-fried) strengths the Stomach and aids digestion. Ze Xie (Rhizoma Alsmatis Orientalis) eliminates dampness by promoting diuresis. Hua Shi (Talcum) and Sheng Gan Cao (Radix Glycyrrhizae) are ingredients of Six-one Powder (Liu Yi San 六一散) that eliminates summer-heat and promotes diuresis.

Eliminate Dampness in the Stomach with Sclerotium Poriae Cocos Decoction (Chu Shi Wei Ling Tang 除湿胃苓汤)

The four herbs, Cang Zhu (Rhizoma Atractylodis), Hou Pu (Cortes Magnoliae Officinalis), Chen Pi (Pericarpium Citri Reticulatae) and Sheng Gan Cao (Radix Glycyrrhizae) are the ingredients of the formula, Calming the Stomach Powder (Ping Wei San 平胃散) which has the function of drying dampness,
regulating qi and harmonising the Spleen and Stomach. Zhu Ling (Polypours), Ze Xie (Rhizoma Alsmatis Orientalis) and Chuan Mu Tong (Caulis Clematidis Armandii) eliminate dampness by promoting diuresis. Fu Ling (Sclerotium Poriae Cocos) and Bai Zhu (Rhizoma Atractylodis) strengthen the Spleen and eliminate dampness. Hua Shi (Talcum), Zhi Zi (Fructus Gardeniae) and Deng Xin Cao (Medulla Junci Effusi) clear heat and promote diuresis. Fang Feng (Radix Ledebouriellae Divaricatae) expels wind and stops itch. Rou Gui (Cortex Cinnamomi) balances the cold property of other herbs.

c) Yin Deficiency with Blood Dryness

i. Clinical features:

Typical AE symptoms and signs plus dry and thickened skin with scaling, red or dark red tongue body with scanty silver, peeled tongue coating, deep and thready pulse.

ii. Principle of treatment:

Nourish Yin, replenish blood and moisten dryness

iii. Formula:

Modified Radix Rehmanniae Glutinosae Decoction (Di Huang Yin Zi 地黄饮子)

iv. Prescription:

Shu Di Huang (Radix Rehmanniae Glutinosae Preparata) 30g
Dang Gui (Radix Angelicae Sinensis) 12g
He Shou Wu (Radix Ploygoni Multiflori) 15g
Sheng Di Huang (Radix Rehmanniae Glutinosae) 12g
Xuan Shen (Radix Scrophulariae Ningpoensis) 12g
Mu Dan Pi (Cortex Moutan Radicis) 12g  
Hong Hua (Flos Carthami Tinctorii) 12g  
Jiang Can (Bombyx Batryticatus) 8g  
Bai Ji Li (Fructus Tribuli Terrestris) 12g  
Sheng Gan Cao (Radix Glycyrrhizae) 6g  

v. Explanation:  
Shu Di Huang (Radix Rehmanniae Glutinosae Preparata), Dang Gui (Radix Angelicae Sinensis) and He Shou Wu (Radix Ploygoni Multiflori) replenish blood. Sheng Di Huang (Radix Rehmanniae Glutinosae) and Xuan Shen (Radix Scrophulariae Ningpoensis) nourish Yin. Mu Dan Pi (Cortex Moutan Radicis), Hong Hua (Flos Carthami Tinctorii) and Jiang Can (Bombyx Batryticatus) invigorate blood circulation and open channels. Bai Ji Li (Fructus Tribuli Terrestris) expels wind and stops itch. Sheng Gan Cao (Radix Glycyrrhizae) harmonises actions of other herbs.

2.13.2 Topical Application of CHM for AE  
Unlike oral application of CHM, topical application of CHM is used based on different skin lesions rather than syndrome identification (Gu & Huang, 1993).  
Formulae listed below in the form of topical administration are recommended for AE or infantile eczema:  
a. Herbal ointments:  
i. Formula:  
Indigo Naturalis Ointment (Qing Dai Gao 青黛膏)  
ii. Prescription:  
Qing Dai (Indigo Naturalis) powder 75g
Vaseline 300g

iii. Function:
Clear heat and toxin, moisten skin and stop itchiness.

iv. Indication:
Children aged between 1 to 6 months with eczema.

b. Herbal powder:
i. Formula:
Indigo Naturalis Powder (Qing Dai San 青黛散)

ii. Prescription:
Qing Dai (Indigo Naturalis) 60g
Shi Gao (Gypsum Fibrosum) 120g
Hua Shi (Talcum) 120g
Huang Bai (Cortex Phellodendri) 60g

iii. Function:
Clear heat and toxin, astringe and stop itchiness.

iv. Indication:
Children in age group of 12 months and above with AE.

2.14 RCTs for Oral Administration of CHM for AE

Zhang and his team conducted a Cochrane systematic review on RCTs using oral Zemaphyte for treatment of AE (Zhang, et al., 2004). Zemaphyte was a commercial mixture with 10 Chinese medicinal herbs. It has been no longer available on market since 2004 as the manufacturer was unable to obtain license to produce the mixture. The product was composed of Fang Feng (Ledebouriella Seseloides), Wei Ling Cai (Potentilla Chinensis), Chuan Mu Tong (Clematis Armandii), Sheng Di Huang (Rehmannia Glutinosa), Shao Yao (Paeonia Lactiora), Dan Zhu Ye (Lophatherum...
Gracile), Bai Xian Pi (Dictamnus Dasycarpus), Bai Ji Li (Tribulus Terrestris), Gan Cao (Glycyrrhiza Uralensis), and Jing Jie (Schizonepeta Tenuifolia). Three RCTs using Zemaphyte for adults or children with AE were conducted in 1990’s and year 2000 in UK and another trial with the same products was completed in Hong Kong in year 1999. Three trials were randomised placebo controlled cross-over designs, consisting of two phases with eight weeks for each phase, and assessing the Zemaphyte with inert plants as placebo. There were total 159 participants aged from one to 60 years in those included trials. The drop-out rates ranged from 7.5% to 22.5% and no trial used intention-to-treat (ITT) analysis. In two of these three trials the reduction in erythema and skin damage was greater in the intervention group than in placebo, and participants showed improvement in sleeping and expressed a preference for Zemaphyte. One trial also reported that participants in the intervention group experienced less itchiness. But one trial reported there were no differences between the Zemaphyte and placebo. A fourth trial in year 1999 conducted in Hong Kong was an open-label design to evaluate Zemaphyte in a freeze dried granules form with the same ingredients of Zemaphyte in herbal form in 18 participants with AE. There was a similar effect in the two different forms of preparation of the product. The reviewers concluded that Chinese herbal mixtures may be effective in the treatment of AE. The reviewers also pointed out that there were only four small, and low quality RCTs of the same product identified in their review and the clinical outcomes were heterogeneous.

Another randomised, double-blind, placebo-controlled clinical trial using an oral CHMs concoction was published in 2007 (K. Hon, et al., 2007). A total of 85 patients aged from five to 21 years with moderate-to-severe AE (objective SCORAD > 15) were recruited in February 2004 to July 2005. The authors claimed there was a significant improvement in QoL with measurement of the CDLQI in the intervention group compared with patients receiving placebo at the end of the three-month treatment and
four weeks after stopping treatment \((p = .008 \text{ and } .059 \text{ respectively})\). Number of days of using topical corticosteroid was also reduced in intervention group \((p = .003)\) in comparison with the placebo group \((p = .289)\). The total amount of topical corticosteroid used was significantly decreased by one-third in the intervention group at month four of the trial in the intervention group in comparison of what in the placebo group \((p = .024)\). Although SCORAD score fell from 58.3 to 49.7 in the intervention group \((N = 42; p = .003)\) in comparison of baseline, there was no significant difference compared to the placebo group which was also observed a reduction of the score from 56.9 to 46.9 \((N = 43; p = .001)\). The concoction contained five Chinese medicinal herbs: Jin Yin Hua (Flos Lonicerae) 2g, Bo He (Herba Menthae) 1g, Mu Dan Pi (Cortex Moutan) 2g, Cang Zhu (Rhizoma Atractylodis) 2g, and Huang Bai (Cortex Phellodendri) 2g with a total of 9 grams of raw herbs. Dosage of CHM was three capsules of the formula twice daily for a period of 12 weeks in the trial. The investigators concluded that the CHM preparation is effective in improving QoL and reducing topical corticosteroid use in children with moderate-to-severe AE.

2.15 Comments

A syndrome (Zheng 证) in CM is a pathological conclusion of a disease, in which its causes, features e.g. cold or heat type and location (interior or exterior) in a certain period of time are included. In the framework of holistic conception, identification of a syndrome is more radical than that of a disease. A disease (Bing 病) is a conclusion of full prognosis of a disorder in the body including characteristics (symptoms and signs) and rules of a disorder in CM point of view (Deng & Guo, 1987). For instance, “Wind of the four fossae (Si Wan Feng)” is a disease in CM. It then can be subcategorised into different syndromes such as: Accumulation of interior damp-heat, Spleen deficiency with excess dampness and Yin deficiency with blood dryness according to
various associated symptoms and signs manifested on an individual. Pertained to the principle of “Determination of treatment based on syndrome identification (Bian Zheng Lun Zhi 辨证论治)”, a single disease of “Wind of the four fossae” should be individually treated with different Chinese herbal formulae as outlined on Section 2.13.1. Definition of “Wind of the four fossae” in CM diagnosis is not completely covering the main clinical features of AE as its description was only for the skin lesions on the legs and ankles with monthly relapse. Further, syndrome identification of “Wind of the four fossae” relies on those non-specific symptoms and signs such as bowel movements such as constipations or diarrhoea, colour of urine, tongue and pulse readings. The accuracy of the syndrome identification is in doubt as it is determined by those non-specific symptoms and signs which could be seen in other diseases and vary from time to time during the course of a disease. Inconsistence and bias of syndrome identification are also inevitable and substantial as the collection of those symptoms and signs mostly depend on clinician’s personal experience or clinical skills. As a syndrome identification is determined on those non-specific symptoms and signs appearing during the process of a disease, a disease in CM like “Wind of the four fossae” or AE could be further subcategorised into different syndromes based on clinician’s assessment criteria. Consequently the disease could be treated with different Chinese herbs (Zhou & Li, 2008). Thus, there is a need for evaluation of effectiveness of CHM for AE as well as establishment of validated Chinese medicine syndromes of AE based on evidence with statistical significance.

In summary, although the Cochrane systematic review of CHM for AE conducted by Zhang and his team in 2004 found that a certain CHM product might be efficacious for AE; results among the included trials were conflicting. RCT conducted by Hon and his colleagues in 2007 demonstrated that the CHM concoction was effective in improving QoL and reducing usage of topical steroid in children. In regarding the
AE skin lesion, the treatment intervention used in Hon’s report did not show significant difference to what in the controlled group. Both the Cochrane systematic review and Hon’s RCT only dealt with oral applications of CHM for AE. Scientific evidence of efficacy and safety of topical application of CHM for AE is absent; therefore there is a need to seek for such evidence through a systematic review.
Chapter 3  Methods

This chapter describes the methodology used in the systematic review and development of a protocol for a pilot randomised double-blinded placebo-controlled clinical trial for topical application of CHM for AE.

Section I: Methodology of Systematic Review

This systematic review follows the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions 5 (the Handbook) (The Cochrane Collaboration, 2008).

3.1 Search Strategies

3.1.1 Electronic Searches

The following electronic databases were searched in February, March and October 2008 when this program was conducted for identifying studies to be included in the review:

- Cochrane Skin Group Ongoing Skin Trials Register (up to 2008)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (up to 2008)
- CINAHL (EBSCO) (1982-2008)
- mRCT (1998 – 2008)
• ProQuest (1938 – 2008)
• PubMed (1966-2008)

In addition, the following Chinese databases were searched:
• VIP Information (cqvip.com) (1989-2008)
• China National Knowledge Infrastructure (cnki.net) (1979-2008)

The sample strategies used for searching in MEDLINE (OVID) are listed as below:

# 1. randomized controlled trial.pt.
# 2. controlled clinical trial.pt.
# 3. randomized.ab.
# 4. placebo.ab.
# 5. clinical trials as topic.sh.
# 6. randomly.ab.
# 7. trial.ti.
# 8. #1 or #2 or #3 or #4 or #5 or #6 or #7
# 9. (animals not (human and animals)).sh.
#10. #8 not #9
# 11. dermatitis/ or exp dermatitis atopic/ or exp eczema/ or exp neurodermatitis/
# 12. besniers prurigo.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
# 13. prurigo.mp.
# 14. exp drugs chinese herbal/
# 15. exp traditional medicine chinese/
Similar search strategies plus “infantile eczema” or “childhood eczema” were applied to other databases.

3.1.2 Hand-searches

The following CM journals and conference proceedings were hand-searched:

- Congress proceedings of the First World Congress on Chinese Medicine (Melbourne 2003)
- Congress proceedings of the Third International Congress of Traditional Medicine (Toronto 2006).
3.1.3 Unpublished Studies

Clinicians or dermatologists and experts in CM were contacted for unpublished RCTs.

3.1.4 Study Selection

Two reviewers, Sherman Gu (SG, the candidate) and Angela Yang (AY, supervisor) independently screened the titles and abstracts of all identified studies according to the inclusion and exclusion criteria. If there was insufficient information in the titles or abstracts, the full text of the studies were retrieved for further information. Any discrepancy between the two reviewers was discussed with a third party Chun Guang Li (CL, senior supervisor) or Charlie Xue (CX, consultant).

3.2 Inclusion and Exclusion Criteria

3.2.1 Types of Studies

All RCTs, with or without blinding, published in English or Chinese languages were included. For cross-over studies, only data from the first treatment phase was included.

3.2.2 Types of Participants

All patients with AE were considered regardless of age, gender and ethnic group. AE must be diagnosed according to internationally recognised criteria such as the Hanifin and Rajka criteria (J. M. Hanifin & Rajka, 1980) or the UK refinement (H. C. Williams, et al., 1994) when the terms "atopic eczema" or "atopic dermatitis" were used in the articles. In the absence of explicit diagnostic criteria, studies for adult participants diagnosed with "eczema" or "chronic eczema" were excluded. However,
studies for children (new born to 16 years old) diagnosed with "eczema" by physicians or dermatologists were included as diagnosis of infantile eczema or childhood eczema is equivalent to AE as discussed on Section 2.1 of Chapter 2.

3.2.3 Types of Interventions

We included topical applications of CHM (manufactured or clinician self-designed Chinese medicinal formulae) if they were compared with the following control interventions: placebo, no intervention, acupuncture, or conventional medicines (drugs).

We excluded trials with a combination of topical and oral CHM interventions or a combination of topical application of CHM and drugs or a combination of topical application of CHM and other therapy such as acupuncture.

3.2.4 Types of Outcome Measures

RCTs were included if at least one of the following primary or secondary outcome measures was used:

3.2.4.1 Primary Outcomes

a) Percentage of trial participants with at least good or excellent improvement in terms of investigator score. Both short-term (within six weeks) and long-term (seven weeks or more) improvement were included.

b) Percentage of trial participants with at least good or excellent improvement in terms of participants/parents self-rated score. Both short-term (within six weeks) and long-term (seven weeks or more) improvement were included.

3.2.4.2 Secondary Outcomes
a) Changes in participants/parents self-rated improvement in SCORAD, EASI, or SASSAD as stated in each of the trials in both short-term (within six weeks) and long-term (seven weeks or more) improvement.

b) Changes in participants/parents self-rated improvement in QoL both short-term (within six weeks) and long-term (seven weeks or more) improvement.

c) Adverse events.

### 3.3 Data Extraction

Data were extracted by using a data extraction form developed by the Cochrane Skin Group which has been modified to suit this review (Appendix 1). Data from each selected study consisted of the number of events ($n$) and participants ($N$) in individual patient data for dichotomous data and number of participants ($N$), mean, and standard deviation (SD) for continuous data. Extracted data also consisted of the treatment and controlled interventions, outcome measures and adverse events. Two reviewers SG and AY independently extracted the data. When the information in the published article was insufficient, the investigators of the studies were contacted.

### 3.4 Assessment of Risk of Bias of Included Studies

SG and AY independently assessed the risk of bias of included studies with the items which consist of the domains of:

a) randomisation,

b) sequence generation,

c) allocation concealment,

d) blinding of participants, personnel and outcome assessors,

e) items of incomplete outcome data.
Any discrepancies between the two reviewers were resolved by the third party CL and CX through discussion. All corresponding authors of included studies were contacted by mails for clarification of the data such as study design, method of randomisation and statistic data when needed (Appendix 2).

3.5 Data Analysis

Meta-analyses were conducted by using the RevMan 5 software (The Cochrane Collaboration, 2008).

3.5.1 Data Synthesis and Measures of Treatment Effect

It was anticipated that the nature of the interventions could be quite diverse, and it was, therefore, unlikely that they would all estimate the same treatment effect. Indeed, the included studies in our review expressed different, yet related, intervention effects, and for this reason, we conducted a random-effects model when attempting to pool data from included studies. We planned that if substantial heterogeneity was found (I² statistic greater than 50%), then we would explore the sources of such heterogeneity by rechecking the data, and by subgroup analysis based on clinical and methodological diversity factors. If the presence of substantial heterogeneity could not be explained, we would not undertake statistical pooling.

3.5.2 Heterogeneity of Included Studies

The heterogeneity of included studies was interpreted through the characteristics of interventions. It was assessed by using I² statistic, which describes the percentage of variation across studies due to heterogeneity rather than by chance. The effect size analysis was conducted to explore the differences between interventional groups. Dichotomous data were tested by Mantel-Haenszel with random-effects analysis model.
and expressed as risk ratios (RR) with 95% confidence intervals (CI). When sufficient data were available, continuous data were presented as difference of means (MD) with 95% CI when all studies used the same measurement scale or as standardised mean differences (SMD) with 95% CI if different scales were used to measure the same outcome and \( p < .05 \) was regarded as significant.

3.5.3 Reporting Bias

Reporting bias was assessed by testing funnel plot asymmetry as recommended on Section 10.4.3.1 of the Handbook if there were more than 10 trials included in the meta-analysis.

3.5.4 Subgroup Analysis

We planned to perform subgroup analyses under the heading of "Children (16 years old or under) with AE versus Adult with AE", and "Application of Intervention Based on Chinese Medicine Syndrome Differentiation versus Non-individualisation Formula" where there are at least moderate levels of heterogeneity across the included studies. We proposed to investigate the sources of heterogeneity including participant factors e.g. age, diagnosis, sex, race, co-morbidity, treatment factors e.g. dosage, formulation, and study factors e.g. concordance rates, quality of reporting, and quality control for the Chinese herbal preparations e.g. source, purity, preparation facilities to explain such differences.

3.5.5 Sensitivity Analysis

We planned to perform sensitivity analyses of the primary outcomes by excluding studies with high risk of bias. Where substantial heterogeneity exists between studies for the primary outcome (\( I^2 \) statistic > 50%), sources for such
heterogeneity such as diagnosis of the disease, composition or dose of the herbal medication should be sought and explored in sensitivity analyses.

3.5.6 Report of Adverse Events and Dealing with Missing Data

We planned to report studies relating to adverse events quantitatively. We also planned to apply ITT analysis to the included study if there are any missing data.

3.6 Studies with Multiple Treatment Groups and Unit of Analysis Issues

We planned to select the intervention group that is most relevant to the systematic review if studies involve multiple treatment groups.

We considered unit of analysis issues if a study involves measurements on different body parts such as comparison of a site on one arm versus another site on the other arm for topical interventions. In this case, we would treat the study as a "within patient trial" and we would perform separate meta-analysis as appropriate.

For cross-over trials where participants were given different treatments in random sequence, we planned to undertake a separate meta-analysis. The results from the first treatment phase might be combined with those from the parallel trials if data are available, then we proposed to combine the data from included parallel studies and the treatment phase of included cross-over studies in the meta-analysis. We also planned to include cross-over studies only if their methods were appropriate as suggested by the Handbook.

Section II: Methodology of Protocol for a Pilot RCT

A protocol for pilot randomised double-blind placebo-controlled clinical trial for topical application of CHM for AE was developed. This protocol was prepared
according to the guidelines of *Australian Clinical Trial Handbook* issued by Therapeutic Goods Administration (TGA), Department of Health and Ageing, Australian Government (TGA, 2006) and follows the “Nine CONSORT Checklist Items For RCTs of Herbal Medicines” recommended by the Consolidated Standards of Reporting Trials (CONSORT) Group (Gagnier, et al., 2006). Key elements for conducting a good quality RCT such as randomisation, sequence generation, allocation concealment, blinding methods, proper sample size, compliance with protocol, determination of baseline and endpoint as well as adequate outcome measures have been well addressed. Details of the protocol are presented on Chapter 5.
Chapter 4   Results I - Systematic Review

This chapter reports the findings of the systematic review which was based on the rigorous methodology specified in Chapter 3. It also discusses the findings and makes recommendations for future research.

4.1 Selection of Studies

4.1.1 Search Results

There were 164 potential studies identified. The number of studies identified from each database is summarised in Table 3.

Table 3: Summary of Search Results

<table>
<thead>
<tr>
<th>Database</th>
<th>Date of Search</th>
<th>Number of the Potential Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Skin Group: Ongoing Skin Trials Register (up to 2008)</td>
<td>08/02/2008</td>
<td>10</td>
</tr>
<tr>
<td>The Cochrane Central Register Of Controlled Trials (CENTRAL) (up to 2008)</td>
<td>06/03/2008</td>
<td>12</td>
</tr>
<tr>
<td>PubMed MEDLINE (1966-2008)</td>
<td>06/03/2008</td>
<td>17</td>
</tr>
<tr>
<td>cqvip.com (1989-2008)</td>
<td>24/10/2008</td>
<td>68</td>
</tr>
<tr>
<td>cnki.net (1979-2008)</td>
<td>29/10/2008</td>
<td>31</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td>164</td>
</tr>
</tbody>
</table>

4.1.2 Screening of Studies

Among the potential 164 studies, 129 were excluded after screening the titles and abstracts with various reasons which included non-topical applications of CHM ($N = 40$), review/protocol ($N = 48$), non-clinical study ($N = 9$), treatment intervention combined with conventional medicines ($N = 4$), non-RCT ($N = 13$) and duplicated publication ($N = 15$). Full texts of the rest 35 papers were retrieved and 26 studies were
excluded due to either absence of controlled group, or oral application of the treatment intervention, or topical treatment intervention combined with oral application of CHM or drugs or acupuncture, or non-AE study. Of the other nine studies, we performed a test of meta-analysis to measure consistency of outcomes across the studies and found that the $I^2$ statistic was greater than 50% which indicated heterogeneity. We then reassessed the data of those nine studies and found that six of them were quasi-randomised or pseudo-randomised studies according to the definition outlined in Box 13.4a of the Handbook. Numbers of participant in the treatment group were much greater than those in the control group in those six studies. Therefore, only three studies finally met the criteria and were included in this review. Reasons for the exclusion of those six papers are provided in Table 4 Characteristics of excluded studies. The study selection process is shown in Figure 3.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Reasons of Exclusion</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu 2000</td>
<td>ALLOCATION: Quasi-randomised</td>
<td>(Fu, 2000)</td>
</tr>
<tr>
<td>He 2000</td>
<td>ALLOCATION: Quasi-randomised</td>
<td>(He, Li, &amp; Ding, 2000)</td>
</tr>
<tr>
<td>Li 2005</td>
<td>ALLOCATION: Quasi-randomised</td>
<td>(H. M. Li, 2005)</td>
</tr>
</tbody>
</table>
4.2 Characteristics of Included Studies

The summary of characteristics of included studies is provided in Table 5.
Table 5: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Diagnostic criteria</th>
<th>Sample size</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma 2007</td>
<td>Parallel group, control study</td>
<td>Did not state</td>
<td>Grade I: erythema with millet sized papules. Grade II: bleeding, ulcer and discharges. Grade III: crustae and decrustation CM subcategory: not stated</td>
<td>Treatment 38, 2 to 24 months, Control 30, 2 to 24 months</td>
<td>Treatment: Zi Cao oil Ingredients and dosage: Zi Cao (Radix Arnebiae) 200g, Ma You (Oleum Sesami) 500g. Route of administration: External application of the oil 3 to 5 times per day Duration of treatment: 7 days Follow-up: 6 to 12 months after the treatment and there were 9 cases relapsed Control: Topical usage of calamine lotion 3 to 5 times daily for 7 days. Follow-up: 6 to 12 months after the treatment and there were 19 cases relapsed</td>
</tr>
<tr>
<td>Nie 2002 Parallel group, control study</td>
<td>Did not state</td>
<td>Skin lesions such as rashes, papules, erythema, blisters, yellowish scales and crustae, discharges and erosion that distributed on face and the rest of the body</td>
<td>CM subcategory: not stated</td>
<td>160, 2 to 12 months</td>
<td>149, 2 to 12 months</td>
</tr>
<tr>
<td>Yang 2007</td>
<td>Parallel group, control study</td>
<td>Did not state</td>
<td>1. Children with obesity or malnutrition, skin lesions such as rashes, erythema, blisters, yellowish and whitish scales and crustae on the cheek, face, head and the rest of the body; 2. Severe pruritus resulted to loss of sleep, poor appetite; 3. Skin lesions associated with discharges and erosions or secondary infection CM subcategory: not stated</td>
<td>40, 1 to 24 months</td>
<td>35, 1 to 24 months</td>
</tr>
</tbody>
</table>

Note: $N =$ number of participants
4.2.1 Types of Studies

All three included studies (Ma 2007; Nie 2002 and Yang 2007) were randomised controlled parallel clinical studies with topical application of CHM for infantile eczema or childhood eczema. All of them were conducted in China and published in Chinese. None of them used blinding design. No included studies were cross-over trials. Descriptions of each included studies were detailed in Section 4.3.

4.2.2 Types of Participants

A total of 452 participants aged from one month to two years old and diagnosed with infantile eczema or childhood eczema by clinicians were recruited in these studies. Sample sizes of these included studies ranged from 68 to 309. Diagnostic criteria for the skin condition were set by the clinicians in included studies and none of these studies reported exclusion criteria. Although the studies did not use international recognised diagnostic criteria for AE for recruitment of participants, we included these studies for systematic review because their clinical diagnoses were considered to be equivalent to the definition of AE as described in Section 2.1, 2.10 and 2.11 of Chapter 2, and met the inclusion criteria stated in Section 3.2.2 of Chapter 3. None of these studies differentiated the condition according to the CM syndrome identifications.

4.2.3 Types of Interventions

There are three different Chinese herbal formulae used as treatment interventions in the three included studies. All of them used self-designed formulae (Zi Ni Fang 自拟方). One study (Ma 2007) applied CHM oil topically. One study (Yang 2007) used CHM powder directly on the affected areas and the other one (Nie 2002) employed moist dressing of CHM on the surface of the skin lesions.
A total of 15 Chinese herbs with botanical and mineral origins including Zi Cao (Radix Arnebiae), Ma You (Oleum Sesami), Di Yu (Radix Sanguisorbae), Ma Chi Xian (Herba Portulacae), Huang Lian (Rhizoma Coptidis), Huang Bai (Cortex Phellodendri), Cang Zhu (Rhizoma Atractylodis), Wu Bei Zi (Galla Chinensis), He Zi (Fructus Chebulae), Ku Fan (processed Alumen), Qing Dai (Indigo Naturalis), Shi Gao (Gypsum Fibrosum), Hua Shi (Talcum), Ku Shen (Radix Sophorae Flavescentis) and Lu Gan Shi (Calamina) were used in included studies. These Chinese herbs were under the categories of “Heat-clearing”, “Damp-resolving”, “Damp-draining”, “Hemostatic”, “Astringent”, and “Externally applied and miscellaneous” in Chinese materia medica (Z. J. Li, 2008). All included studies used different herbs in their treatment intervention except Huang Bai (Cortex Phellodendri) which was used in two included studies.

In terms of control interventions, all included studies used conventional medicines. For example, one study (Ma 2007) used calamine lotions, one study (Yang 2007) used antihistamine and calcium and another study (Nie 2002) used varieties of controlled intervention including penicillin, corticosteroid creams and chlorpheniramine.

Treatment durations ranged from three to 10 days in included studies. All studies reported follow-up data after the last treatment. Follow-up periods were six and 12 months respectively in two studies (Ma 2007; Yang 2007) and another one did not state when the follow-up was performed (Nie 2002).

4.2.4 Types of Outcome Measures

Two studies (Ma 2007 and Yang 2007) used percentage of treated patients with improvement of skin lesions and less itching with the terms of “recovery”, “significant improvement” and “effective” as their primary outcome measures. One study (Nie 2002) used percentage of treated patients with improvement of skin lesions with the terms of “significant improvement” and “effective” as its primary outcome measures.
None of the included studies used scoring system such as SCORAD, EASI or SASSAD for measuring the severity of the condition. QoL was not assessed in any included studies. Table 6 summarises the outcome measures in included studies.

Table 6: Summary of Outcome Measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Number of Evaluation (N) in Treatment Group</th>
<th>Number of Evaluation (N) in Controlled Group</th>
<th>Number of Event (n) in Treatment Intervention</th>
<th>Number of Event (n) in Controlled Intervention</th>
<th>Statistic used and p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching Relief</td>
<td>Ma 2007 (N=68)</td>
<td>38</td>
<td>30</td>
<td>36</td>
<td>20</td>
<td>t-test and Chi-square test (χ² = 7.565 ). p &lt; .05</td>
</tr>
<tr>
<td></td>
<td>Yang 2007 (N=75)</td>
<td>40</td>
<td>35</td>
<td>37</td>
<td>23</td>
<td>Did not state. p &lt; .01</td>
</tr>
<tr>
<td>Itching Relief and Improvement of Skin Lesions</td>
<td>Ma 2007 (N=68)</td>
<td>38</td>
<td>30</td>
<td>36</td>
<td>20</td>
<td>t-test and Chi-square test (χ² = 7.565 ). p &lt; .05</td>
</tr>
<tr>
<td></td>
<td>Nie 2002 (N=309)</td>
<td>160</td>
<td>149</td>
<td>160</td>
<td>89</td>
<td>Did not state. p &lt; .01</td>
</tr>
<tr>
<td></td>
<td>Yang 2007 (N=75)</td>
<td>40</td>
<td>35</td>
<td>37</td>
<td>23</td>
<td>Did not state. p &lt; .01</td>
</tr>
</tbody>
</table>

Note:  
- n = number of events  
- N = number of participants
4.3 Description of Individual Studies

4.3.1 Ma 2007 (Ma & Li, 2007)

Ma’s study reported that 68 children with infantile eczema, aged from two to 24 months were randomised into treatment group (N=38) and control group (N=30). Chinese herbal oil (Zi Cao You 紫草油) was used three to five times daily for seven days on the treatment group. Calamine lotion was used for comparison. Both diagnosis and outcome measures were set by the clinicians who claimed a total effective rate of 94.7% in intervention group (36/38) and 70% in control group (20/30) (p < .05). Incidentally, it was discovered that the final number used for analysis in the control group was actually 29 even though the initial claim was 30. The authors stated that the efficacy of Zi Cao You was superior to that of calamine lotion for treatment of infantile eczema.

4.3.2 Nie 2002 (Nie, 2002)

Nie’s study provided CHM lotion (Formula was unnamed) to 160 patients who were diagnosed with childhood eczema and aged from two to 12 months in the intervention group. The lotion was applied to the affected skin for 30 minutes once per day for three to five days. Diagnosis and outcome measures were determined by the clinician who assessed symptoms and signs of patients. Intramuscular injection of penicillin, topical usage of cortisone creams and oral intake of chlorpheniramine were used in control group with 149 cases. The author claimed that there was a 100% of the total effective rate in CHM lotion group (160/160) and 61.07% in control group (91/149). Rate of relapse was measured with 42.50% in CHM lotion group (68/160) and 90.11% in control group (82/149). The author claimed that there was statistical
significance between the two groups with respect to the total effective rate and relapse rate \( (p < .01) \).

4.3.3 Yang 2007 (S. M. Yang, 2007)

Yang’s study reported there were 40 children aged from one to 24 months with infantile eczema in the intervention group and there were 35 children with the same age range in control group. CHM power (formula was unnamed) was used externally three to four times per day for seven to 10 days. Oral intakes of antihistamine and vitamin B complex, calcium tablets were used in control group. Diagnosis and outcome measures were set by the clinician who claimed there was 92.50% total effective rate in intervention group and 65.71% in control group \( (p < .01) \). The author concluded that efficacy of the CHM powder was significantly superior to that of antihistamine and vitamin B complex, calcium tablets for treatment of infantile eczema.

4.4 Assessment of Risk of Bias on Included Studies

Risk of bias in all three included studies were classified as “unclear” with the items which consist of the domains of randomisation, sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, and items of incomplete outcome data. These were due to lack of relevant data on the published papers of those included studies. The graph of the assessment is shown in Figure 4.
All authors claimed that their study was “randomised controlled clinical study”. However, none of them provided methods of randomisation and how the random number was allocated to the groups. No included studies reported blinding when the studies were conducted. There was a missing datum in Ma’s study (Ma & Li, 2007); the missing datum was not addressed by the author. Letters for further information of randomisation method, allocation concealment, blinding, incomplete outcome data and statistic method were sent to the corresponding authors of the included studies but none of them replied. There was insufficient information such as unreported findings to determine bias relating to the selective reporting. The summary for risk of bias of the each included study is shown in Figure 5.
4.5 Treatment Effects of Topical Application of CHM for AE

As the interventions of included studies used different categories of CHMs that are different in nature, and consequently producing different effects, it was, therefore, unlikely that these studies would all estimate the same treatment effect. For this reason, we used RevMan 5 statistical method of Mantel-Haenszel with random-effects analysis model to pool data from included studies for estimate their overall effects.

### 4.5.1 Percentage of Trial Participants with “Effective” Improvement in Skin Itching Relief

Ma’s study (Ma & Li, 2007) and Yang’s study (S. M. Yang, 2007) reported skin itching relief as their outcome measures. Ma’s study expressed the degree of itching...
relief as “recovery”, “significant” and “effective” in both CHM and control groups. Yang’s study expressed as “significant” and “effective” in both CHM and control groups. We combined the figures on “recovery”, “significant” and “effective” and expressed as “total effective rate of skin itching relief” and analysed the overall effect by comparing topical application of CHM with the controlled intervention (conventional medicines). The forest plot of comparison showed that topical application of CHM significantly relieved skin itchiness (RR 1.41, 95% CI 1.18 to 1.70); Z = 3.70 (p = .0002) compared with controlled intervention (Figure 6). P = 0%.

Figure 6: Comparison of the Outcome of Total Effective Rate of Skin Itching Relief between Topical Application of CHM and Controlled Intervention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CHM</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma 2007</td>
<td>36</td>
<td>38</td>
<td>30</td>
<td>1.42 [1.09, 1.85]</td>
</tr>
<tr>
<td>Yang 2007</td>
<td>37</td>
<td>40</td>
<td>23</td>
<td>1.41 [1.09, 1.82]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>78</td>
<td>65</td>
<td>100.0%</td>
<td>1.41 [1.18, 1.70]</td>
</tr>
<tr>
<td>Total events</td>
<td>73</td>
<td>43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%

Test for overall effect: Z = 3.70 (P = 0.0002)

Foot note: “Total effective rate of skin itching relief” is a sum of the skin itching relief rate expressed as “recovery”, “significant” and “effective” by the authors of the included studies.

4.5.2 Percentage of Trial Participants with “Effective” Improvement of Skin Lesions

Nie’s study (Nie, 2002) reported improvement of skin lesions as its outcome measure and expressed the improvement as “significant” and “effective” in both CHM and control groups. Ma’s study (Ma & Li, 2007) and Yang’s study (S. M. Yang, 2007) reported skin itching relief as well as improvement of skin lesions as their outcome measures. Ma’s study expressed the degree of itching relief and improvement of skin lesions as “recovery”, “significant” and “effective” in both CHM and control groups.
Yang’s study expressed as “significant” and “effective” in both CHM and control groups. We combined the figures on “recovery”, “significant” and “effective” and expressed as “total effective rate of improvement of skin lesions” and analysed the overall effect by comparing topical application of CHM to controlled intervention. The forest plot of comparison showed that topical application of CHM significantly improved the skin lesions (RR 1.56, 95% CI 1.40 to 1.73); \( Z = 8.27 \) \((p < .00001)\) compared to controlled interventions (Figure 7). \( I^2 = 0\% \).

Figure 7: Comparison of the Outcome of Total Effective Rate of Improvement of Skin Lesions between Topical Application of CHM and Controlled Interventions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CHM</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Ma 2007</td>
<td>36</td>
<td>38</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Nie 2002</td>
<td>160</td>
<td>160</td>
<td>91</td>
<td>149</td>
</tr>
<tr>
<td>Yang 2007</td>
<td>37</td>
<td>40</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>238</td>
<td>214</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \text{ Tau}^2 = 0.00; \text{ Chi}^2 = 1.61, \text{ df} = 2 (P = 0.45); I^2 = 0\% \)

Test for overall effect: \( Z = 8.27 (P < 0.00001) \)

4.5.3 Heterogeneity of Included Studies

Dichotomous data (total effective rate of outcome measure) were tested by Mantel-Haenszel with random-effects analysis model and expressed as RR with 95% CI. There was no heterogeneity identified among the included studies as \( P = 0\% \) across the three included studies.

4.5.4 Reporting Bias

Reporting bias was not assessed by method stated on Section 3.5.3 of Chapter 3 as there were only three studies included in the meta-analysis.
4.5.5 Subgroup Analysis

No subgroup analysis was performed as there was no heterogeneity across the included studies and participants in all included studies were children and application of intervention was not based on CM syndrome differentiation.

4.5.6 Sensitivity Analysis

No sensitivity analysis was tested as there was no heterogeneity across the studies for the outcome measures ($I^2$ statistic < 50%).

4.5.7 Summary of Effects across the Included Studies

We used the *Grades of Recommendation, Assessment, Development and Evaluation* (GRADE) system recommended by the Handbook to assess level of evidence on outcome measures.

Table 6 lists the main outcome measures used by the included studies. Improvement of skin lesions was used as main outcome measure in all included studies. Two studies (Ma & Li, 2007; S. M. Yang, 2007) also measured skin itching in conjunction with improvement of skin lesions as outcome measure. Neither score index for measurement of AE severity such as SCORAD, EASI, SASSAD nor score of QoL was employed as outcome measures in any of the included studies. As mentioned on Section 4.3.1, the final number used in analysis was one less than that initially quoted in Ma’s study i.e. 30 becomes 29. It is not clear if this missing datum was an oversight or dropout. If it was due to dropout, then there was no attempt by the authors to conduct an ITT.
Table 6: Summary of Effects across the Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measures</th>
<th>Statistic Method and p value</th>
<th>Effect Size Risk Ratio [95% CI]</th>
<th>Level of Evidence</th>
</tr>
</thead>
</table>
| Ma 2007    | 1. Itching relief and rashes disappeared completely (recovery): 8/38  
2. Itching significantly relief and rashes disappeared > 60% (significant): 16/38  
3. Itching relief and rashes disappeared 20%-30% (effective): 12/38  
4. No itching relief and rashes disappeared < 20% (ineffective): 2/38 (1. + 2. + 3. = 36/38) | t-test and Chi-square test ($\chi^2 = 7.565$). $p < .05$                                        | 1.42 [1.09, 1.85]                        | Low, unclear risk of bias with serious limitations in the design and implementation (lack of allocation concealment and blinding) |
| Nie 2002   | 1. Skin lesions disappeared with small scales (significant): 130/160  
2. Skin lesions improved (effective): 30/160  
3. Skin lesions not improved (ineffective): 0/160 (1. + 2. = 160/160) | Did not state statistic method. $p < .01$                                                    | 1.63 [1.44, 1.86]                        | Low, unclear risk of bias with serious limitations in the design and implementation (lack of allocation concealment and blinding) |
| Yang 2007 | 1. Itching relief completely and skin lesions disappeared completely within 7 days (significant): 25/40  
2. Itching relief and skin lesions disappeared within 10 days (effective): 12/40  
3. Itching and skin lesions not relief after 10 days (ineffective): 3/40 (1. + 2. = 37/40) | 1. Itching relief completely and skin lesions disappeared completely within 7 days (significant): 9/35  
2. Itching relief and skin lesions disappeared within 10 days (effective): 14/35  
3. Itching and skin lesions not relief after 10 days (ineffective): 12/35 (1. + 2. = 23/35) | Did not state statistic method.  
$p < .01$ | 1.41 [1.09, 1.82] | Low, unclear risk of bias with serious limitations in the design and implementation (lack of allocation concealment and blinding) |

Note: $n = \text{number of events}$  
$N = \text{number of participants}$
4.6 **Adverse Events**

None of the included studies provided any information on adverse events in their studies. Thus, meta-analysis could not be performed to evaluate the safety of topical application of CHM for AE.

4.7 **Studies with Multiple Treatment Groups and Unit of Analysis Issues**

None of the included studies have more than two intervention sites. No study involved measurements on different body parts such as comparison of a site on one arm versus another site on the other arm.

4.8 **Discussion and Recommendations**

4.8.1 **Summary of Results**

This is the first systematic review with stipulated methodological features for evaluation of effectiveness and safety of topical application of CHM for AE. All three included studies used Chinese medicinal substances for treatment of infantile eczema or childhood eczema and made comparison of the outcome measures with various types of controlled interventions. The included studies used clinician rated outcome such as skin lesions and patient self-rated outcome i.e. skin itching as primary outcome measures.

Authors of the three included studies all claimed that there were statistical significant differences between the treatment group and control group, and effects of treatment interventions were always superior to what in the controlled interventions.
4.8.2 Strength of the Evidence

All included studies had moderate sample size ($N > 50$) with a total of 452 participants. The included studies were designed as parallel controlled clinical studies where controlled interventions were used for comparison of measurement of effectiveness of the treatment interventions.

4.8.3 Weakness of the Evidence

All of the included studies were of low quality and associated with several major methodological weaknesses. For example, although all included studies used randomisation for grouping of participants, none of them stated method of randomisation. When we requested further information from the corresponding authors of the included studies, none of them responded. Inadequate randomisation could give rise to an investigator’s bias for grouping of participants; consequently affecting the outcomes (J. P. Liu, 2006). The absence of using validated outcome measure instruments such as the SCORAD, EASI or SASSAD in the included studies made quantifiable data analysis almost impossible (Eichenfield, et al., 2003). In this review the three studies happened to use different diagnostic, inclusion and exclusion criteria as well as different herbal formulae. Furthermore, there were “unclear risks of bias” with serious limitations in the design and implementation such as lack of allocation concealment, blinding, and quantitative assessment of outcome in the included studies; therefore, it is difficult to draw a conclusion if topical application of CHM was effective to relieve skin itching and improve skin lesion in infantile eczema or childhood eczema because of the above-mentioned weaknesses.
Even though all included studies claimed that there were statistical significant differences in the outcome measures on CHM treatment groups compared with those in the control groups; however, due to low level of evidence strength and risks of bias with serious limitations assessed by the GRADE system, these claims could not be taken for granted. In addition, we doubted the claim of 100% effective rate on treatment group reported by Nie’s study (Nie, 2002). Although no adverse events were reported in the three included studies, data were unavailable for evaluation of their safety.

4.8.4 Applicability of the Evidence

As pointed out above in Section 4.8.3, there were numerous deficiencies that contributed to the overall low qualities of the included studies, thus more RCTs with rigorous methodological designs are needed to confirm the efficacies or otherwise.

4.8.5 Suggestions for Future Studies

Topical administration of medicines has a few advantages over the oral application of medicines. These include protecting the skin directly by using cream or other vehicle, removing the medication from the affected area immediately in case of an adverse reaction happened, and is particularly user-friendly in paediatric practices (R. H. Yang, 2005). Evidence of effectiveness and safety of CHM for AE needs to be confirmed by RCT; in this regard, we identified three clinical studies, which employed topical application of CHM, and met the pre-set inclusion criteria from 164 potential studies. Among these three studies, two studies used one common Chinese herb, Huang Bai (Cortex Phellodendri). Pharmacological investigations demonstrated that Huang Bai possesses anti-inflammatory effect (Shen, 2000) which may help to explain some of
its effectiveness in treating AE. Such promising pharmacological properties need to be confirmed by RCT, the gold standard for evaluating therapeutic benefits of interventions. Although the three reviewed articles showed promising results, however, due to the low level of evidence strength, this review did not provide convincing statistical support for efficacy of CHM used topically for AE or infantile eczema or childhood eczema. Therefore, well-designed, adequately powered, randomised controlled clinical trials are needed to evaluate the efficacy and safety of topical use of CHM for managing AE.
Chapter 5  Results II - Protocol for a Pilot RCT of Topical Application of CHM for AE

This chapter reports development of a protocol for a pilot RCT of topical application of CHM for AE based on the methodological methods stated in Section II, Chapter 3.

5.1 Information

5.1.1 Recommendations from the Systematic Review

Further to the discussion in Chapter 4, a properly designed double-blind RCT is recommended to evaluate the efficacy and safety of CHM for the treatment of AE through topical administration. Thus a protocol for a pilot RCT was developed in this thesis.

5.1.2 Description of Intervention used in the Trial

In this trial, the investigators will evaluate the efficacy and safety of an existing Chinese herbal formula named Modified Qingdaisan by topical administration for treatment of AE in children and adults through a randomised double-blind placebo-controlled clinical trial. Qingdaisan (Indigo Naturalis powder) has been used for skin conditions in children and adults for at least 27 years in CM practice (Y. R. Wang & Wang, 1979). As stated on Section 2.13.2 of Chapter 2, this formula is one of the routine topical CHM formulae for AE and infantile eczema. The proposed treatment intervention name as modified Qingdaisan is composed of five ingredients, which are listed along with their active chemical components (Shen, 2000; L. H. Zhao, 2005) in Table 7 below.
## Table 7: Ingredients of Modified Qingdaisan

<table>
<thead>
<tr>
<th>Pharmaceutical Name</th>
<th>Medicinal Name in Latinate Form</th>
<th>Chinese Pin Yin</th>
<th>Chinese Character</th>
<th>Active Chemical Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigo Naturalis</td>
<td>Baphicacanthus cusia Qing Dai</td>
<td>青黛</td>
<td>Indican, Indirubin</td>
<td></td>
</tr>
<tr>
<td>Rhizoma Coptidis</td>
<td>Coptis chinensis Huang Lian</td>
<td>黄连</td>
<td>Berberine, Coptisine, Worenine</td>
<td></td>
</tr>
<tr>
<td>Gypsum Fibrosum</td>
<td>Calcium sulfate Shi Gao</td>
<td>石膏</td>
<td>CaSO$_4$$\cdot$2H$_2$O</td>
<td></td>
</tr>
<tr>
<td>Cortex Moutan</td>
<td>Paeonia suffruticosa Mu Dan Pi</td>
<td>牡丹皮</td>
<td>Paeonol, Paeonoside, Paeonolide, Paeoniflorin</td>
<td></td>
</tr>
<tr>
<td>Rhizoma Anemarrhenae</td>
<td>Anemarrhena asphodeloides Zhi Mu</td>
<td>知母</td>
<td>Mangiferin, Timosaponin Sarsasapongenin, Markogenin, Anemarans,</td>
<td></td>
</tr>
</tbody>
</table>

The above medicinal substances are listed on the Therapeutic Goods Administration Approved Terminology for Medicines (TGA, 1999). All of the substances are traditional Chinese herbs and have been used safely for hundreds of years. None of them are listed on the “The List of Prohibited Chinese Medicine Herbs in Victoria” issued by the Drugs and Poisons Unit of the Department of Human Services of Victoria on 24 March 2006 ([http://cmrb.vic.gov.au/information/schedherbs.html#list](http://cmrb.vic.gov.au/information/schedherbs.html#list), accessed on 31 July 2011) nor in the Standard for the Uniform Scheduling of Medicines and Poisons No 1 (the SUSMP 1)(TGA, 2010). No adverse reactions have been reported in other clinical studies in which the interventions contain these herbs (W. Z. Chen, 2003). The five medicinal substances will be in the form of herbal extract granules provided by a Good Manufacturing Practice (GMP) licensed company with a concentration of five to one ratio (i.e. five grams of raw herbs equivalent to one gram of herbal granules). This formula will be in a 5% of cream with 95% of Polyethylene glycol (PEG) 1000 and will be administered topically twice daily for eight weeks in the trial. As stated on Section 2.1 of Chapter 2, AE is a chronic inflammatory superficial skin disease; most of the active chemical components from this proposed CHM intervention have anti-inflammatory action. For instance, Mangiferin in Zhi Mu (Rhizoma
Anemarrhenae), Berberine in Huang Lian (Rhizoma Coptidis), Paeonol in Mu Dan Pi (Cortex Moutan), Isdirubin and Indigo pure in Qing Dai (Indigo Naturalis), all have the action of suppression of allergy (Shen, 2000) and Calcium in Shi Gao (Gypsum Fibrosum) has the action of maintenance of the physiological function of the macrophage (Yin & Guo, 1994).

5.1.3 Statement of Compliance

Once the protocol is approved by the RMIT Human Research Ethics Committee (HREC), the trial will be registered on Clinical Trial Notification (CTN) at TGA and the Australian New Zealand Clinical Trials Registry (ANZCTR) at the NHMRC Clinical Trials Centre. This trial will be conducted strictly in compliance with the protocol, the principles of Good Clinical Practice (GCP) and relevant requirements.

5.2 Trial Objectives

The primary objective of this pilot study will be evaluating whether the topical application of CHM can effectively reduce severity of symptoms and signs and improve the QoL in children and adults with AE. It will also assess the safety of the topical application of CHM for AE. The secondary objective of this trial is to determine an appropriate sample size and dosages for future large scale RCT studies.

5.3 Trial Design

The pilot study will be a 14-week randomised double-blind placebo-controlled clinical trial to evaluate the efficacy and safety of topical application of a CHM cream for moderate to severe AE in children or adults. The 14 weeks comprise of two weeks baseline, eight weeks treatment phase, and four weeks follow-up period. Figure 8 illustrates the flowchart of the study.
Figure 8: Flowchart of the Trial

Recruit participants by advertisement or referrals

Record demographic information and provide forms to potential participants (PPs)

PPs complete and return forms to investigator

**Screening period**
PPs will be invited for initial assessment if eligible

**Baseline period**
Pre-eligible PPs wait for two weeks for washout and eligible PPs are included if the 2nd baseline Objective SCORAD score is ≥ 15

Randomised participants (N=64)

Randomised to treatment intervention group (N=32)

Randomised to control intervention group (N=32)

CHM cream **Treatment period** (N=32)

Placebo cream **Treatment period** (N=32)

Visit 1 (Week 3), 2 (Week 5), 3 (Week 7), 4 (Week 9)
Participants receive intervention products and instruments and being assessed on each visit

Visit 5 (Week 11)
Collect all instruments and other responses

End of trial

Final data collection and analysis

Possible early withdrew/dropout (N=?)

Complete CHM cream treatment

Possible early withdrew/dropout (N=?)

Complete placebo cream treatment

Follow-up (Visit 6 on Week 14)
Participants return instruments by mail
5.4 Randomisation

Block randomisation method will be employed with four participants a block, two participants will receive the real treatment and the other two will be treated with inert cream (the placebo). Randomisation code will be calculated via Microsoft Excel in “Function and Rand”. Stratified randomisation will be employed as per their age and those who are aged from 12 months to 16 years old will enter the children subgroup and those who are over 16 year old will be in the adult subgroup.

5.5 Blinding

Neither participants nor investigators will know if the participant is receiving real treatment or placebo. Randomised numbers will be generated by an independent statistician using Excel program. The numbers will be randomly assigned into real treatment group and placebo group, and sealed into individual opaque envelopes, which will be allocated by a central officer who is unaware of participants’ details. Envelopes were sequentially numbered and opened only after participant’s IDs were written on the envelope. In the initial visit after baseline period, each participant will be asked to pick one sealed envelope from the pack of all the envelopes. The envelopes will be opened by a CHM dispenser, who could be a registered CHM practitioner or registered CHM dispenser. The CHM dispenser then hands over the container with CHM cream or inert cream (the containers are identical in appearance and labeled) to the participant and gives the participant an oral and written instruction (Appendix 3) of method of usage of the cream. The CHM dispenser will record information including participant’s ID, sequential number of the container and randomisation code on a Record Sheet of Dispensary (Appendix 4) independently for future data analysis. The code will not be broken to participants and personnel who are involved in data entry and data analysis.
5.6 Interventions

5.6.1 Treatment Intervention

The CHM cream (treatment intervention) will be prepared by an appointed manufacturer with GMP certificate. PEG 1000 will serve as vehicle for both the intervention and placebo groups. Table 8 lists compositions of those Chinese medicinal extracts in each container filled with 50 grams of PEG 1000 cream.

Table 8: Compositions of the Chinese Herbal Medicine Cream

<table>
<thead>
<tr>
<th>Pharmaceutical Name</th>
<th>Botanical Name</th>
<th>Chinese Pin Yin</th>
<th>Chinese Characters</th>
<th>Compositions (Per 50 Grams of PEG 1000 Cream)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigo Naturalis</td>
<td>Baphicacanthus Cusia</td>
<td>Qing Dai</td>
<td>青黛</td>
<td>2 grams</td>
</tr>
<tr>
<td>Rhizoma Coptidis</td>
<td>Coptis Chinensis</td>
<td>Huang Lian</td>
<td>黄连</td>
<td>1 gram</td>
</tr>
<tr>
<td>Gypsum Fibrosum</td>
<td>Calcium Sulfate</td>
<td>Shi Gao</td>
<td>石膏</td>
<td>1 gram</td>
</tr>
<tr>
<td>Cortex Moutan</td>
<td>Paeonia Suffruticosa</td>
<td>Mu Dan Pi</td>
<td>牡丹皮</td>
<td>1 gram</td>
</tr>
<tr>
<td>Rhizoma Anemarrhenae</td>
<td>Anemarrhena Asphodeloides</td>
<td>Zhi Mu</td>
<td>知母</td>
<td>1 gram</td>
</tr>
</tbody>
</table>

The cream will be packaged in a plastic container with a label including the following information: Clinical trial external use only, apply the cream on the affected skin twice daily, keep out of reach of children, expiry date, the manufacturer, batch number and brief information of the trial (Appendix 5).

5.6.2 Control Intervention

A placebo will be applied to the control group. PEG 1000 will also serve as the vehicle in the placebo. The smell, colour and apparent package of placebo will be as close to the treatment interventional cream as possible.

The treatment or placebo cream will be applied by the participant or guardian on the participant’s affected skin lesion twice daily for eight weeks. During this trial after the baseline period, the participants will be asked to come back to the trial centre for assessment.
fortnightly that is on day 15, day 29, day 43, day 57 and day 71. Day 71 is also the endpoint of the usage of the intervention products (both the CHM creams and placebo). Day 99 will be the last day of the four weeks of follow-up period and the trial will be concluded on Day 99. Application of the creams should be stopped when any adverse reaction is notified either by participant, guardian or investigator.

5.7 Selection and Withdrawal of Participants

Participants will be recruited through advertisement (Appendix 6) via local papers, posters, internet, organisations and referrals from general practitioners (GPs) or dermatologists. Contact details of the potential participants will be recorded during their initial enquires and expression of interest in the trial (Appendix 7). A Plain Language Statement (PLS) with information of the trial including the purpose of the trial, about the intervention, potential adverse reaction and ethical issues will be given to potential participants (Appendix 8). All potential participants or their guardians will be provided with Informed Consent Forms (Appendix 9 and 10) and General Information Questionnaires (Appendix 11). Potential participants will be interviewed and evaluated with the criteria of inclusion and exclusion (Appendix 12) in order to select suitable participants for the trial (Screening period).

5.7.1 Selection Criteria

- Inclusion Criteria

The U.K. Working Party’s diagnostic criteria will be adapted for inclusion in this trial (C. Charman, et al., 2003; H. C. Williams, et al., 1994).

I. Diagnosis of the condition:

   a) History of skin pruritus in the last 12 months plus three or more of the any followings;
b) History of flexural involvement;

c) Visible flexural dermatitis;

d) Onset under the age of two (not used for children under four years old);

e) Age: 12 months or above;

f) Personal history of atopy such as asthma, allergic rhinitis or hay fever;

II. Severity of AE

Baseline objective SCORAD score $\geq 15$ (moderate to severe) in two baselines measurements in interval of two weeks;

III. Completion of informed consent forms.

- Exclusion Criteria

  a) Those who have used corticosteroids or any preparation of CHM or other herbs for treatment of AE orally in the past 30 days;

  b) Those whose skin condition has been diagnosed with scabies or allergic contact dermatitis or seborrheic dermatitis or psoriasis;

  c) Age: less than 12 months;

  d) Those who are currently pregnant;

  e) Those who have renal or liver dysfunction

5.7.2 Withdrawals and Dropouts

Without providing reasons, participants are allowed to withdrawal at any time during the trial. However, withdrawal (dropout) of participant will be followed up to investigate the time and reason of withdrawal (Appendix 13). Principle of ITT with worst scenario will be used in the final data analysis for any withdrawn participant or missing data (D. Wang & Bakhai, 2006).
5.7.3 Discontinuers

Participant will be advised to discontinue the treatment if there is a product-related adverse event or if the participant was not compliant i.e. using corticosteroid orally during the treatment period. Using corticosteroid topically is allowed for those participants who have been using corticosteroid topically before participating the trial and whose skin conditions are worsen during the trial treatment period. However, same drug and dosage of the drug should be recommended and medicinal record will be well documented. All discontinuers will not be replaced by new participants. Principle of ITT with worst scenario will be used in the final data analysis for any missing data from discontinuers.

5.8 Sample Size

There is lack of statistic evidence for topical application of CHM for AE in RCTs with high quality. This proposed trial is to test the efficacy of an intervention. Our hypothesis will, therefore, be that there is difference in the proportion of improvement between the intervention and control groups. Calculation of the participant numbers is based on the following formula (Bulpitt, 1983):

\[
N = \frac{K [P1 (1- P1) + P2 (1- P2)]}{(P1-P2)^2}
\]

Set \(N\) be the minimum number for each of the two groups.

Set \(P1\) be the proportion of the outcomes on the control group. The proportion is estimated as 20%. This estimation is based on the fact that the vehicle on the control group is made of PEG 1000, and there is no evidence PEG 1000 could improve the conditions in AE patients. Thus the \(P1\) in sample size calculation formula is 0.20.

Set \(P2\) be the proportion of the outcomes on the herbal intervention group. Since there are no previous publications of RCTs with similar herbal cream, for the purpose of this trial a
60% effectiveness is set as satisfactory target which is sufficient to distinguish significant difference between control and intervention. The intervention group will be \([(60\%) - (20\%)]\n= 40\% improvement at the end point, then P2 is 0.40.

Set K be the square of the standardised normal deviate for type III error or \(r\) (\(r\) assumes the final better treatment is actually the worse treatment, in this proposed trial the type III error or \(r\) is very small). If \(r\) is set at 5\%, then \(K = 1.64^2 = 2.7\).

\[
N = \frac{2.7 \left[0.20 \times (1- 0.20) + 0.40 \times (1- 0.40)\right]}{(0.20 - 0.40)^2}
\]

Thus, \(N = 27\).

Set estimated dropout rate is 20\%, then \(N = 27 \times 0.20 + 27 \approx 32\)

There will be 32 participants for treatment intervention and placebo control group respectively with a total of 64 participants to be included based on the above calculation. For future trials, more accurate sample size will be re-calculated based on the results of actual proportion of outcomes obtained from this pilot study.

5.9 Baseline and Treatment Periods

When pre-eligible participants are selected, there will be 14 days of washout period. At the beginning of this period, SCORAD will be measured, and at the end of 14 days, they will be re-measured if the initial objective SCORAD score is 15 or greater. The baseline period will also be considered as the screening period as only those participants who have 15 or more objective SCORAD score in two weeks interval might go into the treatment periods. In order to test a hypothesis that the CHM cream is effective for treatment of AE regardless the different subcategories classified under the CM differentiation of syndrome, participants will be given a *Chinese Medicine Syndrome Identification for AE instrument* (Appendix 14) and assessed by a registered CHM practitioner for CM differentiation of syndrome at the
screening stage. A folder with Case Report Forms (Appendix 15) will be set up for each participant.

Treatment periods: Apply the intervention products twice daily for eight weeks.

Endpoint: on Day 71 (week 11) of the application of the intervention products or when an adverse reaction has been reported and nature of the adverse reaction has been evaluated by the investigator.

5.10 Outcome Measures

5.10.1 Measurements of SCORAD and QoL Index

Efficacy of the treatment intervention and placebo will be evaluated via the changes of severity of the condition which will be measured by using the SCORAD including its subjective and objective items (Stalder & Taieb, 1993) (Appendix 16 and 17). QoL index score such as the IDQOL (M.S. Lewis-Jones, et al., 2001) for children under four years old (Appendix 18); the CDLQI for children from age five to 16 (M. S. Lewis-Jones & Finlay, 1995) (Appendix 19) and the DLQI (Finlay & Khan, 1994) for adults (Appendix 20) will also be measured. Permissions of using these instruments of QoL assessment for the trial have been provided by the authors.

5.10.2 Primary and Secondary Outcome Measures

Changes in the subjective items, which will be expressed as VAS score and the objective items of the SCORAD score at the end of the treatment will be used as primary outcome measures. Changes of the QoL index score at the end of the treatment will be used as secondary outcome measures. The baseline measure for the SCORAD score and QoL index score will be set on the initial record at the screening period. Both the SCORAD score and QoL index score will be measured at the endpoint. The QoL index score will be recorded
at the screening period and at the end of the treatment period respectively. A *Daily Medical Record Sheet* will be given to the participants or their guardians to record the details of administration of the intervention products and self-rated symptoms and signs. This daily record will also record the usage of any other forms of medications with their names and dosage (Appendix 21). Participants or guardian’s self-rated symptoms (itchiness) and signs (redness, dryness or thickness of the skin) recorded in the *Daily Medical Record Sheets*, and the *VAS Sheets* will be used as primary outcome measures.

Outcome measures will be assessed and recorded on an *Outcome Measures Sheet* (Appendix 22) at each appointed time when the participants visit the trial centre. The intervention products will not be given any more at the fifth visit on Day 71 of the trial and participants will be advised to stop using the intervention products one day before Day 71 of the trial (endpoint).

5.10.3 Assessment of Safety

Safety of the intervention products will be monitored by way of any adverse reactions observed by the participants and their guardians or the trial investigator. Blood sample of participants will be collected by an appointed registered nurse at the screening period and at the fifth visit of the trial for full blood test, IgE level, liver and renal function tests (Appendix 23). Blood tests will be authorised by an appointed medical officer and conducted in RMIT clinical trial centre.

Once receiving an adverse event report, participant will be advised to discontinue the usage of the intervention products and the trial investigator will examine the participant immediately. Details of the adverse event will be recorded on *Adverse Event Questionnaires* (Appendix 24) and medical advice from the medical officer will be given to any case with serious adverse reaction.
In case of any adverse events or reactions, the investigator will manage such events or reactions in compliance with the guidelines of “Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)” issued by TGA (TGA, 2000). A serious adverse event will be reported within 72 hours and adverse event will be reported within 15 days.

5.10.4 Assessment of Participant Compliance

Participant compliance will be monitored each time when participants revisit the trial centre (Appendix 25). Four weeks after the end of treatment period, participants will be followed up for further outcome measurements. Table 9 summaries the schedule of the trial and provide a summary list for primary and secondary outcome measures.
Table 9: Schedule of the Trial

<table>
<thead>
<tr>
<th>Items</th>
<th>Title of the Documents</th>
<th>Screening Period</th>
<th>Baseline and Washout Period</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5 (Endpoint)</th>
<th>Visit 6 (Follow-up)</th>
</tr>
</thead>
</table>
| Demographic information taking | 1. Record Sheet for Potential Participants  
2. Participant Information Sheet                                                       |                        | Day 1 to 14 Week 1 and 2    | Day 15 Week 3 | Day 29 Week 5 | Day 43 Week 7 | Day 57 Week 9 | Day 71 Week 11     | Day 99 Week 14       |
| Informed consent forms       | 1. Prescribed Consent Form for Persons Participating in Research Projects Involving Interviews, Questionnaires or Disclosure of Personal Information  
2. Prescribed Consent Form For Persons Participating In Research Projects Involving Tests and/or Medical Procedures |                        | +                           |               |               |               |               |                   |                     |
| General medical history taking | 1. General Information Questionnaires  
2. Inclusion/Exclusion Criteria                                                        |                        | +                           |               |               |               |               |                   |                     |
<p>| CM syndrome identification   | Chinese Medicine Syndrome Identification for AE                                        |                        | +                           |               |               |               |               |                   |                     |
| Blood tests                  | Pathology Tests                                                                         |                        | +                           |               |               |               |               |                   |                     |</p>
<table>
<thead>
<tr>
<th>Items</th>
<th>Title of the Documents</th>
<th>Screening Period</th>
<th>Baseline and Washout Period</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5 (Endpoint)</th>
<th>Visit 6 (Follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective SCORAD</td>
<td>Assessment Form for Objective Score of SCORAD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Subjective SCORAD</td>
<td>VAS for Assessment of Severity of AE</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>QoL score</td>
<td>1. IDQOL 2. CDLQI 3. DLQI</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Distributions of treatment or placebo intervention cream</td>
<td>Record Sheet of Dispensary</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily medical record</td>
<td>Daily Medical Record Sheet</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor of adverse event</td>
<td>Adverse Event Questionnaires</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance check</td>
<td>1. Record Sheet of Treatment 2. Record Sheet of Withdrawal/Dropout of the Participants</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.11 Statistics

Data will be analysed by using *Statistical Package for the Social Services* version 16.0 by an independent statistician. Comparison of continuous variables (i.e. SCORAD scores) between baseline and endpoint within the intervention group, and between the intervention and placebo groups will be expressed as MD with 95% CI. Wilcoxon test will be performed for comparison of dichotomised data (i.e. “improved”) and will be expressed as RR with 95% CI. All comparisons will be made in two-tailed and *p*-values < .05 is considered to be statistically significant. ITT analysis will be performed on missing data as stated on Section 5.7.2. Interim analysis and earlier stopping of the trial will be activated once a general serious adverse reaction that may potentially affect the safety of all participants is reported.

5.12 Data Identification and Confidentiality

The participant’s name, gender, date of birth, medical history and contact details will be collected. Participants’ Information will be retained for 15 years, and will be disposed under the guidelines of “*NHMRC (Joint National Health and Medical Research Council) / AVCC (Australian Vice-Chancellor’s Committee) Statement and Guidelines on Research Practice*” (NHMRC, 1997). Data will be kept in a locked file cabinet in the RMIT Trial Laboratory. Only the investigator and his supervisors have access to the data. However, the investigator will permit trial-related monitoring by authorities, review by RMIT HREC, and regulatory inspection, providing direct access to source data/documents for such monitoring, review or inspection.
5.13 Quality Control and Quality Assurance

The intervention products (the CHM cream and placebo) will be manufactured by a GMP licensed company according to the standards set by TGA for therapeutic goods for listed medicines. This includes the identification of raw materials and limit tests of heavy metals and contaminations. In addition, the fingerprint profiles of methanol extracts of the products against reference standards (active chemical components identified from individual herbs) will be established using a Shimadzu HPLC (high performance liquid chromatography) system (model SCL-10Avp HPLC-DAD) combined with a SPD-M10Acp diode array detector, reserve-phase C18 column and gradient elution method. The methanol extract will be prepared using an accelerated solvent extractor ASE 100 (Dionex, USA) under an optimised extraction protocol. A single batch of products will be used for the clinical trial and chemical analysis. A sample of products will be deposited at the RMIT herbal identification and analysis laboratory, WHO Collaborating Centre for Traditional Medicine at RMIT University. The extraction and HPLC analysis will be carried out at RMIT University.

5.14 Trial Investigators and other General Information

The trial investigation team members will come from different academic backgrounds. The trial investigators, who are in charge of history taking, input of inclusion/exclusion criteria questionnaires forms, CM syndrome identification forms will be CM practitioners with at least 10 years clinical experience and must be registered in the Division of Chinese herbal medicine with Chinese Medicine Registration Board of Victoria, Australia. One of the team members will be an expert in herbal pharmacology and one member will be a statistician. A western medicine
and Chinese medicine dermatologist will be appointed for providing expert advice. The trial will be sponsored by Traditional & Complementary Medicine Research Program, RMIT Health Innovations Research Institute and Discipline of Chinese Medicine, School of Health Sciences, RMIT University and authorised by the Head of Discipline and supervisors of the trial. Sponsor’s medical expert (or officer) will be appointed once the protocol is approved. The trial will be conducted at the Clinical Trial Laboratory, Building 202, Discipline of Chinese Medicine, School of Health Sciences, RMIT University, Plenty Road, Bundoora Vic. 3083 Australia.

5.15 Ethics Issues

The investigator will submit an application to RMIT HREC for approval prior to conduction of the trial. The application will encompass all the relevant ethical issues such as risk and benefits of the trial, informed consent, protection of children and confidentiality.

5.16 Publication Policy

Manuscript of the trial report will be submitted to a professional journal for publication once the trial is concluded. None of the information related to the privacy of the participants such as their names or contact details will be released in any publication.

5.17 Financing and Insurance
The sponsor of this trial will arrange financial support for conduction of the trial. The RMIT University will be responsible for public and products liability insurance covering legal liability of the insured to pay damages or compensation in respect of personal injury or damage to property as a result of an occurrence happening in connection with the trial.

5.18 Comments

This protocol outlines the necessity and feasibility for assessing the efficacy and safety of topical application of CHM cream (Modified Qingdaisan) for AE in the form of RCT with a small sample size. A randomised double-blind, placebo-controlled parallel groups clinical trial has been well accepted by research profession as a gold standard method for evaluation of effectives and safety of an intervention (Kane, 2004; Vincent & Furnham, 1997). The primary endpoints will be set on day 71 after the applications of the last dose of intervention products. The trial will be concluded on week 14 of the follow-up period following cessation of application of the intervention creams. In the absence of reliable published RCT information, we proposed to set the endpoint of the trial on Day 71. It is anticipated that results of this pilot study will provide more precise information in deciding outcome measurement time for the endpoint, and appropriate dosage for a larger scale of trial in future.

Recruitment of participants is restricted to the age of 12 months and above to fulfil the diagnostic criteria set by the U. K. Working group. We did not choose the commonly quoted Hanifin’s diagnostic guidelines for the diagnosis of AE because its minor criteria require an ophthalmologist to determine the condition. This is beyond our research resources at this stage. Objective score of SCORAD will be used at screening period for determination of severity of the condition. Only those potential
participants who are assessed with moderate to severe AE for which the objective score of SCORAD is 15 or greater in the interval of two weeks will be included. Therefore, we design a 14-day washout period. At the end of the washout period, the objective score of SCORAD will be measured again. These scores will be used as baseline measures. The objective score of SCORAD will also be used as one of the primary outcome measures and changes of QoL index will be used as secondary outcome measure. Three sets of QoL questionnaires including IDQOL for participants under four years old, CDLQI for five to 16 years old and DLQI for 17 year above will be employed. These three sets of questionnaires for different age groups were developed by the same group of authors from Department of Dermatology Cardiff University, UK and they were designed to be assessing the same parameters using identical quantitative scales while being specific to different age groups, such that results are comparable across all three scales.

This protocol is compiled based on the Checklist Item 4 for Reporting Randomised, Controlled Trials of Herbal Medicine Interventions recommended by the CONSORT Group (Gagnier, et al., 2006). Item 4 includes 4A: Herbal medicinal product name, 4B: Characteristics of the herbal product, 4C: Dosage regimen and quantitative description, 4D: Qualitative testing, 4E: Placebo/control group and 4F: Practitioner. All key issues on the Item 4 have been elaborated in this protocol. For instance, the 4D: Qualitative testing of the intervention products is addressed in Section 5.13.

The ultimate purpose of this pilot trial is to test the efficacy and safety of a designed CHM cream. Further evaluation of the pharmacological action of the CHM cream could be conducted once the potential clinical efficacy is proved by this trial.
The protocol also details the process of the trial and states that the GCP rulings and other guidelines and regulations will be complied. A set of forms including “Plain Language Statement”, “Informed Consents Forms” and “Case Report Forms” are ready for submission for ethics approval by RMIT HREC.
Chapter 6    General Discussion and Conclusion

There are two main components in this thesis. The first one aims at the collection of evidence to assess the efficacy and safety of topical application of CHM for AE by using methodology of Cochrane systematic review. The second component focuses on designing a protocol for a pilot RCT of topical application of CHM for AE.

AE is a common skin disorder in adults as well as in children especially in those aged six to seven years. The prevalence of AE has increased over the last 10 years in worldwide. It is suggested that effective treatment of childhood eczema may prevent the persistence and development of asthma. A consensus of diagnostic criteria and assessment of severity of AE has been well established and validated in conventional (western) medicine, but the standard first-line therapies in conventional medicine for management of AE are not satisfactory. CHM has been used for treatment of AE for years although its efficacy has not been tested with scientific methodology. At present there have been many RCTs evaluating efficacy of oral administration of CHM for AE. Their efficacies have also been reviewed and evaluated through the systematic review published by Cochrane Collaboration. However, there is distinct paucity of information regarding the topical usage of CHM for AE. The systematic review in this thesis is the first one in CHM topical administration for AE, and it has led to the conclusion that existing evidence is far from convincing. Therefore, there is a need to evaluate the efficacy and safety of topical application of CHM for AE by using the methodology of Evidence-based medicine (EBM).

EBM is defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett,
Rosenberg, Gray, Haynes, & Richardson, 1996). The practice of EBM indicates integration of clinician expertise with the best available external clinical evidence which is gained from systematic research. EBM provides scientific standards of evidence for clinical practices where the efficacy of those practices is measurable. Decision marking of applying the most effective techniques or interventions in clinical practices no longer relies on clinician’s accumulated personal experiences, but the scientific evidence that obtained by other researchers (Timmermans & Mauck, 2005). The strength of evidence in EBM is composed of level of evidence, quality and statistical precision of study design. Level of evidence ranks from the top “I degree”, in which evidence is obtained from a systematic review of all relevant RCTs to the bottom “IV degree” where evidence is collected from case series study (NHMRC, 2000). The practice of EBM gives rise to an opportunity for devolvement of traditional Chinese medicine in contemporary context (J. P. Liu, 2006). It is fair to suggest that for CM to be better respected and recognised by the mainstream healthcare system, its practice in terms of effectiveness should be scientifically supported by EBM. Researches of efficacies of CHM by way of EBM approaches such as conducting well designed RCTs that follow the generally accepted gold standards, and systematic reviews of such RCTs as well as laboratory analytical confirmations of the pharmacological properties of Chinese herbs all help to further extend the boundary and theories of, and also promote confidence in traditional Chinese medicine. The systematic review in this thesis is a small contribution to this EBM development of contemporary CM paradigms, and such rapidly burgeoning evidences not only serve to provide more convincing supports to the unique CM practice of syndrome differentiation and treatment principles, but also assist clinicians to treat patients optimally and confidently.
A protocol for a pilot RCT for the purpose of evaluating the efficacy and safety of a CHM cream for AE administrated topically has been developed in this thesis. The trial has been designed to avoid any potential risks of bias in its final outcome measures. Such potential risks of bias are randomisation, sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors and items of incomplete outcome data. The global score system will be employed for primary outcome measures and changes of QoL index as secondary outcome measure. Quality control and assurance of the intervention products has also been addressed to assure the consistent final outcomes of the trial. The RCT will be conducted in compliance with the required ethical standards.

In sum, the systematic review and detailed analysis of the three included studies led to the conclusion of low level of evidence strength. Thus, they did not provide convincing evidential support for effectiveness of CHM used topically for AE or infantile eczema. Therefore, there is a need to evaluate the efficacy and safety of topical application of a CHM formula to treat AE through a well designed randomised double-blind placebo-controlled trial. The trial will be conducted as soon as the protocol is approved by the RMIT HREC.
References


TGA. (2000). *Note for guidance on clinical safety data management: Definitions and standards for expedited reporting (CPMP/ICH/377/95).*


atopic eczema in the international study of asthma and allergies in childhood. *Journal of Allergy and Clinical Immunology, 103*(1 Pt 1), 125-138.


Appendix 1    Data Extraction Form*

(For systematic review of topical application of Chinese herbal medicine for atopic eczema) created by Sherman Gu and commended by Dr Angela Yang on 22 April 2008)

1.       Study ID:

2.       Study Design:

2.1 Design: parallel group   cross over   other (describe)

2.2 Randomization
Was the study described randomised?    Yes / No / Unclear

Evidence:  
Comments:

2.2.1 Sequence generation:
Was the allocation sequence adequately generated?    Yes / No / Unclear

Evidence:  
Comments:

2.2.2 Allocation concealment:
Was allocation adequately concealed?   Yes / No / Unclear

Evidence:  
Comments:

2.2.3 Blinding
Was knowledge of allocated interventions adequately prevented during the study?  Yes / No / Unclear

Evidence:  
Comments:

2.2.4 Incomplete outcome data
Were incomplete outcome data adequately addressed?   Yes / No / Unclear

Evidence:  
Comments:

*The form was adapted and modified from the Data Extraction Form recommended by the Cochrane Skin Group.
2.2.5 Selective outcome report
Are reports of the study free of suggestion of selective outcome reporting? Yes / No / Unclear
Evidence:
Comments:

2.2.6 Topic-specific, design-specific or other potential threats to validity
Was the study apparently free of other problems that could put it at a risk of bias? Yes / No / Unclear
Evidence:
Comments:

3 Participants

3.1 Setting: inpatient / outpatient/ others (describe)

3.2 What are the criteria for patients to join the trial? (describe)

3.3 Age?

3.4 Diagnosis

3.5 Duration of symptoms?

3.6 Other?

<table>
<thead>
<tr>
<th>Number of patients randomised</th>
<th>Intervention 1</th>
<th>Intervention 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4 Withdrawals and dropouts

4.1 ‘Intention to treat’ analysis: Yes / Not stated / No

<table>
<thead>
<tr>
<th></th>
<th>Intervention 1</th>
<th>Intervention 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of withdrawals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number lost to follow up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final number of patients evaluable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.2 Summary: Minimal missing outcome data / ITT unclear? / Substantial missing outcome data

5 Description of interventions

<table>
<thead>
<tr>
<th>Intervention 1</th>
<th></th>
<th>Intervention 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td></td>
<td>Formula</td>
<td></td>
</tr>
<tr>
<td>Ingredients and dosage</td>
<td></td>
<td>Ingredients and dosage</td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td></td>
<td>Route of administration</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment</td>
<td></td>
<td>Duration of treatment</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

6 Outcomes

All data are number of patients, not percentages

<table>
<thead>
<tr>
<th></th>
<th>Intervention 1</th>
<th></th>
<th>Intervention 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End point</td>
<td>Baseline</td>
<td>End point</td>
</tr>
<tr>
<td>Global improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(measured by)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching relief</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(measured by)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Time to remedication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(measured by)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(measured by)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(withdrawal from study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Adverse effects

| Minor |  |

**Assessment of compliance undertaken?**  Yes/ not stated / no

### Comments

Date form completed:

Form completed by:
Appendix 2  Template of Letter to Corresponding Author for Further Information

(English version)

13th May 2008:
Attention:

From:
Mr. Sherman Gu
285 Stud Road, Wantirna South Vic 3152 Australia
Email: sherman.gu@rmit.edu.au

Phone + 613 9925 7635

Dear_____________________ (insert name of the corresponding author here)

Re: Further Information about Your Study

I am writing this letter in regard with request further information about your paper published on ___________________(insert Journal here)________________________ (insert volume, page and year of publication).

I am currently conducting a systematic review as part of my research program at the School of Health Sciences, RMIT University, Australia.

Your paper has met the inclusion criteria. It is assumed that your data might not be published in full due to word limitation of publication, and those unpublished data are important for my research. Therefore, I wonder if you could provide more information about your study.

1. Was your study a randomised controlled study? If yes, please provide information about the method of randomisation, sequence generation and allocation concealment;

2. Did your study involve blinding? If yes, double or single blind? Please provide information of Blinding of participants, personnel and outcome assessors;
3. Did your study have any incomplete data? Please provide any reason if there was any incompletion of treatment. Did you follow up for the uncompleted patient? Did you perform intention-to-treat (ITT) analysis?

4. Details of the statistical methods and data of your study.

Information you provide will be essential for me to get an accurate conclusion of this research program and further enrich the knowledge of Chinese medicine in atopic eczema.

I look forward to hear from you soon.

Yours truly,

Sherman Gu

Encl: (copy of the published paper)
Appendix 3  Instruction of Usage of the Cream

1. Please clean the affected skin with warm clean water, then dry the skin with clean towel before apply the cream on;

2. Open up the sealed container and apply the cream evenly on the affected areas of the skin twice daily (morning and evening);

3. Close the container and store it in a refrigerator;

4. If you feel any adverse reaction after using the cream, please stop using it and call up the trial investigator on (03) 9925 7635 immediately.
Appendix 4 
**Record Sheet of Dispensary**

<table>
<thead>
<tr>
<th>Participant’s ID Number</th>
<th>Sequential Number of the Container</th>
<th>Randomisation Code</th>
<th>Date of Dispensary</th>
<th>Dispenser’s Signature</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
Appendix 5    Template of Label on the Container

For clinical trial externally use only                      Keep out of reach of children

Trial approval code: 
Manufacturer: 
Sponsor: Prof. Charlie Xue                                 Principal investigator: Sherman Gu 
Site: Clinical Trial Laboratory, Building 202, Discipline of Chinese Medicine, 
School of Health Sciences, RMIT University, Plenty Rd., Bundoora Vic 3083 
Quantity: 50 ml                                             Sequential No. 
Instruction: Apply the cream evenly on affected areas twice daily.

Batch No.                                                   Expiry date: 
Participant’s initial:                                      Participant’s ID: 

_________________________________________________________________

Keep the cream refrigerated when not in use. 
Please return the container and any unused cream to investigator at your next visit.
Contact phone number for the trial: Sherman Gu: (03) 9925 7635
Appendix 6  Media Advertisements for Recruitment of Participants

Eczema Sufferers Wanted

Are you or your kid suffering from eczema or dermatitis? Do you concern about the side effects of steroid drugs? If you or your kid are 1 year old or above, and have been diagnosed as eczema, or atopic eczema or atopic dermatitis by a GP or dermatologist, you might be eligible to participate in this clinical trial which involves using traditional Chinese herbal preparation topically for 8 weeks.

The trial has been approved by the appropriate authorities and your personal information will be absolutely confidential.

For more information or to register the trial, please contact A/Prof Chunguang Li on (03) 9925 7635 or email sherman.gu@rmit.edu.au

Mr. Gu is a registered Chinese medicine practitioner in both divisions of Chinese herbal medicine and acupuncture at Chinese Medicine Registration Board of Victoria.

The clinical trial will be conducted at the following venue:

Clinical Trial Laboratory,

Discipline of Chinese Medicine, School of Health Sciences

Building 202, Level 4, Room 46,

RMIT University Bundoora West campus, Plenty Road. Bundoora Vic. 3083
### Appendix 7 Record Sheet for Potential Participants

<table>
<thead>
<tr>
<th>Number</th>
<th>Participant and/or Guardian’ Surname</th>
<th>Given Name</th>
<th>Gender</th>
<th>Postal Address</th>
<th>Date of Birth</th>
<th>Tel: Home</th>
<th>Tel: Business</th>
<th>Mobile</th>
<th>Email Address</th>
<th>PLS* And GIQ** Forms Sent out</th>
<th>Initials and Signature of the Recorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
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</table>

*PLS: Plain Language Statement (Participant Information Sheet)

** GIQ: General Information Questionnaires
Appendix 8  Participant Information Sheet

(Plain Language Statement)*

Date: ______________

Dear ______________

You are invited to participate in a research project being conducted by Traditional & Complementary Medicine Research Program, RMIT Health Innovations Research Institute, & Discipline of Chinese Medicine, School of Health Sciences, RMIT University. This information sheet describes the project in straightforward language, or ‘plain English’. Please read this sheet carefully and be confident that you understand its contents before deciding whether to participate. If you have any questions about the project, please ask one of the investigators listed below.

1. Name of the Trial:

   Pilot Randomised Double-Blind Placebo-Controlled Clinical Trial of Topical Application of Chinese Herbal Medicine for Atopic Eczema

2. Investigators of the Trial:

   Mr. Sherman Gu (Chinese Medicine Master Degree Student)

   A/Prof. Chun Guang Li (Senior project supervisor: Principal research fellow, Chinese Medicine Research Group, chunguang.li@rmit.edu.au, 9925 7635)

   Dr. Angela Wei Hong Yang (Project supervisor: Lecturer, Discipline of Chinese Medicine, anegla.yang@rmit.edu.au, 9925 7175)

   Prof. Charlie Xue (Project consultant: Head, Discipline of Chinese Medicine, charlie.xue@rmit.edu.au, 9925 7745)

* The information sheet was adapted and modified from “Plain language statements and obtaining informed consent of participants – guidelines” RMIT 2004, Document ID r8chsu4o7i2iz.
3. Purpose of the Trial

The Chinese herbal medicine (CHM) cream is an exited external use traditional Chinese herbal preparation for treatment of skin disorders such as eczema or atopic eczema for years. The formula has shown it is effective and safe clinically. There has no side effect or adverse reaction observed so far at the doses that will be tested in this trial. The purpose of this trial is to evaluate the efficacy and safety of this herbal preparation in treatment of atopic eczema with strictly methodological method.

This trial has been approved by the RMIT Human Research Ethic Committee. Mr. Sherman Gu, the chief investigator of the trial, is a registered Chinese medicine practitioner in both divisions of Chinese herbal medicine and acupuncture in the Chinese Medicine Registration Board of Victoria. Mr. Gu was also a clinician in RMIT Complementary Medicine Teaching Clinic from 1999 to 2005. The trial is part of a Master’s degree of Applied Science (Chinese Medicine) supervised by A/Prof. Chun Guang Li, Dr. Angela Yang and Prof. Charlie Xue is the consultant to monitor and review the progress of the project.

4. Procedures of the Trial

You have been referred by your health care provider or invited through media advertisement from our project team. It is expected that a total of 64 participants will be recruited. In this trial, you will be interviewed in the trial center and fill out some forms which will record your present skin condition and other information. You might be asked questions, for instance, “Over the last week, how itchy, sore, painful or stinging has your skin been?” The forms will be used at the end of the trial to compare the different of your conditions with the previous information you provided.

The trial is a double-blind trial for atopic eczema, lasting only 14 weeks. The trial will compare a Chinese herbal medicine cream with a placebo (dummy). This means that both you and Mr. Gu will not know whether the cream that you are given to be used topically during the trial will be the herbal cream or a cream that looks identical to the herbal cream but is inactive. You are welcome to examine the test cream sample before deciding whether you want to participate the trial. You will have to apply the cream two times a day for 8 weeks and will not know whether you have received herbal cream or dummy cream until the trial is completed. However, the identity of the cream can be determined immediately if any adverse reaction develops.

You will not be allowed to use any steroid drugs orally during the trial period. If you have to use steroid topically during the trial period, you should record and report the drug that you use. You can continue to use emollients to moisten the dry skin if you have done so before enrolling this trial. There is no need to change your life style or diet during the trial period.

5. Risk
If you are unduly concerned about your responses to any of the questionnaire items or if you find participation in the project distressing, you should contact Sherman Gu as soon as convenient. Mr. Gu will discuss your concerns with you confidentially and suggest appropriate follow-up, if necessary. The herbal formula has been used clinically both in China and Australia for years and there is no evidence to show adverse reaction in relation to the application of the preparation. If there is any serious adverse reaction occurs, you should stop using the Chinese herbal cream immediately and you will be treated promptly.

6. Benefits
The Chinese herbal cream has been shown its effectiveness in treatment of atopic eczema; therefore, your condition might be improved once the full course of treatment completed. Of course, this is not guaranteed or promised and you might not receive the Chinese herbal cream treatment. However, if you are not in the treatment group, then you will be given the same herbal cream to treat the same condition if the herbal cream has demonstrated its effectiveness and safety with 3 months after the trial is completed.

7. Confidentiality of the Records
Information you provide in this trial will be maintained in confidentiality. No identity of any participant in this trial will be disclosed in any public reports or publications. However, for purpose of monitoring, supervision and review of the trial, identified data will be seen by a small number of people such as the project supervisors, consultants and personnel from RMIT Human Research Ethic Committee. Any information that you provide can be disclosed only if (1) it is to protect you or others from harm; (2) a court order is produced; or (3) you provide the researchers with written permission. Storage and disclosure of the information in this trial will be strictly under the guidance of the Australian Government Joint NHMRC / AVCC Statement and Guidelines on Research Practice 1997. The research data will be kept securely at RMIT for a period of 15 years before being destroyed.

8. If Problem Develops
If any serious adverse event or reaction develops, you will receive prompt and appropriate Chinese medicine (CM) attention. It is agreed that the RMIT Complementary Medicine Teaching Clinic will be made available to you. Reasonable CM treatment will be free when provided through the RMIT Complementary Medicine Teaching Clinic. RMIT has in place public and products liability insurance covering legal liability of the insured to pay damages or compensation in respect of personal injury or damage to property as a result of an occurrence happening in connection with the proposed clinical trial.

9. Financial Considerations
There will be no financial benefits to you or your family for participating in this trial.
10. Obtaining Additional Information
You can ask any questions that occur to you at this time or at any time during your participation in the trial. You will be given a copy of this agreement for your own information. You can also contact Mr. Gu on 0419 396 963.

11. Rights as a Participant
You are free to withdraw your consent to participate in this trial at any time without prejudice. If you select to do so, your right to present or future CM care by Mr. Gu or at RMIT Complementary Medicine Teaching Clinic will not be affected. You have the right to have any unprocessed data withdrawn and destroyed, provided it can be reliably identified, and provided that so doing does not increase the risk for the participant. You also have the right to have any questions answered at any time.

Yours sincerely,

Sherman Gu BMed

Signature: ________________________

Chun Guang Li PhD

Signature: ________________________

Angela Wei Hong Yang PhD

Signature: ________________________

Charlie Xue PhD

Signature: ________________________

Any complaints about your participation in this project may be directed to the Executive Officer, RMIT Human Research Ethics Committee, Research & Innovation, RMIT, GPO Box 2476V, Melbourne, 3001.
Details of the complaints procedure are available on the ‘Complaints with respect to participation in research at RMIT’ page.
Appendix 9 Prescribed Consent Form for Persons Participating in Research Projects Involving Interviews, Questionnaires or Disclosure of Personal Information

<table>
<thead>
<tr>
<th>College</th>
<th>Science, Engineering and Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>School of</td>
<td>Health Sciences</td>
</tr>
<tr>
<td>Name of participant:</td>
<td>Pilot Randomised Control Trial of Topical Application of Chinese Herbal Medicine Cream for Atopic Eczema</td>
</tr>
<tr>
<td>Name(s) of investigators:</td>
<td>(1) Sherman Gu Phone: (03) 9800 3969</td>
</tr>
<tr>
<td></td>
<td>(2) Chun Guang Li Phone: (03) 9925 7635</td>
</tr>
<tr>
<td></td>
<td>(3) Angela Wei Hong Yang Phone: (03) 9925 7175</td>
</tr>
<tr>
<td></td>
<td>(4) Charlie Xue Phone: (03) 9925 7745</td>
</tr>
</tbody>
</table>

1. I have received a statement explaining the interview/questionnaire involved in this project.

2. I consent to participate in the above project, the particulars of which - including details of the interviews or questionnaires - have been explained to me.

3. I authorise the investigator or his or her assistant to interview me or administer a questionnaire.

4. I acknowledge that:

   (a) Having read Plain Language Statement, I agree to the general purpose, methods and demands of the study.

   (b) I have been informed that I am free to withdraw from the project at any time and to withdraw any unprocessed data previously supplied.

   (c) The project is for the purpose of research and/or teaching. It may not be of direct benefit to me.

   (d) The privacy of the personal information I provide will be safeguarded and only disclosed where I have consented to the disclosure or as required by law.

   (e) The security of the research data is assured during and after completion of the study. The data collected during the study may be published, and a report of the project outcomes will be provided to ______________.
(researcher to specify). Any information which will identify me will not be used.

**Participant’s Consent**

<table>
<thead>
<tr>
<th>Participant:</th>
<th>Date:</th>
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<tbody>
<tr>
<td>(Signature)</td>
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<table>
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<tr>
<th>Witness:</th>
<th>Date:</th>
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<td>(Signature)</td>
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</table>

**Where participant is under 18 years of age:**

I consent to the participation of _______________________________ in the above project.

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<tr>
<td>(Signatures of parents or guardians)</td>
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<th>Witness:</th>
<th>Date:</th>
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<td>(Witness to signature)</td>
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</tbody>
</table>

Participants should be given a photocopy of this consent form after it has been signed.

Any complaints about your participation in this project may be directed to the Executive Officer, RMIT Human Research Ethics Committee, Research & Innovation, RMIT, GPO Box 2476V, Melbourne, 3001. Details of the complaints procedure are available on the ‘Complaints with respect to participation in research at RMIT’ page.
Appendix 10 Prescribed Consent Form for Persons Participating in Research Projects Involving Tests and/or Medical Procedures

1. I have received a statement explaining the tests/procedures involved in this project.

2. I consent to participate in the above project, the particulars of which - including details of tests or procedures - have been explained to me.

3. I authorise the investigator or his or her assistant to use with me the tests or procedures referred to in 1 above.

4. I acknowledge that:

   (a) The possible effects of the tests or procedures have been explained to me to my satisfaction.
   
   (b) I have been informed that I am free to withdraw from the project at any time and to withdraw any unprocessed data previously supplied (unless follow-up is needed for safety).
   
   (c) The project is for the purpose of research and/or teaching. It may not be of direct benefit to me.
   
   (d) The privacy of the personal information I provide will be safeguarded and only disclosed where I have consented to the disclosure or as required by law.
   
   (e) The security of the research data is assured during and after completion of the study. The data collected during the study may be published, and a report of the project outcomes will be provided to_______(researcher to specify). Any information which will identify me will not be used.
Participant’s Consent

<table>
<thead>
<tr>
<th>Participant:</th>
<th>Date:</th>
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<td>(Signature)</td>
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<th>Witness:</th>
<th>Date:</th>
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<td>(Signature)</td>
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</table>

Where participant is under 18 years of age:

I consent to the participation of ____________________________________ in the above project.

<table>
<thead>
<tr>
<th>Signature:</th>
<th>(1)</th>
<th>(2)</th>
<th>Date:</th>
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<tr>
<td>(Signatures of parents or guardians)</td>
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<th>Witness:</th>
<th>Date:</th>
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<td></td>
<td></td>
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<tr>
<td>(Witness to signature)</td>
<td></td>
</tr>
</tbody>
</table>

Participants should be given a photocopy of this consent form after it has been signed.

Any complaints about your participation in this project may be directed to the Executive Officer, RMIT Human Research Ethics Committee, Research & Innovation, RMIT, GPO Box 2476V, Melbourne, 3001. Details of the complaints procedure are available on the ‘Complaints with respect to participation in research at RMIT’ page.
Appendix 11  General Information Questionnaires

(All Information provided will be strictly confidential abiding to States and Commonwealth statues. Please fill in the form carefully and thoroughly.)

<table>
<thead>
<tr>
<th>Title: _______</th>
<th>Family Name: __________________________</th>
<th>Given Name: _______________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth: _____________</td>
<td>Occupation: __________________________</td>
<td>Gender: Female  Male</td>
</tr>
<tr>
<td>Address: __________________________________________</td>
<td>Postcode: ____________</td>
<td></td>
</tr>
<tr>
<td>Phone: ___________________(Home) ____________________(Work) ____________________(Mobile)</td>
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<tr>
<td>Email address: ______________________________________________________________________</td>
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</tbody>
</table>

Do you have any known Allergies?  No  Yes ______________________________(Please indicate)

Please list previous illness, accidents and surgeries: ______________________________________

Do you or any of your family members have **atopic eczema, asthma or allergic rhinitis**?

Please list your current medical conditions and medications: ____________________________

Your Medicare Number: ________________ Your family doctor: ___________________________

How do you come to know this trial?

| Family or Friends | Media | Internet | Others ______________________________(Please indicate) |

Signature: ______________________________(Guardian if applicable) Date: ___________________
Appendix 12  Inclusion/Exclusion Criteria
(Screening Instruments)

Instructions:
This form should be completed by a trial investigator with consultation of the participant or his/her guardian on the screening stage of the trial. An eligible participant must be in keep with Criterion 1 plus at least 3 out of Criteria 2 to 6 and all of Criteria 7, 8 and 9 of the Inclusion criteria.

<table>
<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you have a history of skin itchiness in the last 12 months</td>
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</tr>
<tr>
<td>2</td>
<td>Do you have history of flexural involvement</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>Do you have flexural dermatitis</td>
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<tr>
<td>4</td>
<td>Did the skin condition start under 2 years old (not used for children under 4 years old)</td>
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<td>5</td>
<td>Are you 12 months or 12 months above</td>
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<tr>
<td>6</td>
<td>Do you have history of atopic disorders, such as asthma, allergic rhinitis or hay fever</td>
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<tr>
<td>7</td>
<td>First baseline objective SCORAD score $\geq 15$</td>
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<tr>
<td>8</td>
<td>Second baseline objective SCORAD score $\geq 15$ (in an interval of 2 weeks)</td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td>Have you signed the informed consent form and expressed your compliance with the requirements of the trial</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Exclusion Criteria</strong></th>
<th>Questions</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Have you been using corticosteroids orally in the past 30 days</td>
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<tr>
<td>2</td>
<td>Have you been using any preparation of Chinese herbal medicines or other herbs for treatment of the skin eczematous changes orally in the past 30 days</td>
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<tr>
<td>3</td>
<td>Have you been diagnosed by dermatologist with scabies for your present skin condition</td>
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<td>4</td>
<td>Have you been diagnosed by dermatologist with allergic contact dermatitis for your present skin condition</td>
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<td>5</td>
<td>Have you been diagnosed by dermatologist with seborrheic dermatitis or psoriasis for your present skin condition</td>
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<tr>
<td>6</td>
<td>Have you been diagnosed by dermatologist with psoriasis for your present skin condition</td>
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</tr>
<tr>
<td>7</td>
<td>Are you less than 12 months old</td>
<td></td>
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<tr>
<td>8</td>
<td>Are you currently pregnant</td>
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<tr>
<td>9</td>
<td>Do you have any history of renal dysfunction</td>
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<tr>
<td>10</td>
<td>Do you have any history of liver dysfunction</td>
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</table>
Appendix 13  Record Sheet of Withdrawals/Dropouts of the Participants

<table>
<thead>
<tr>
<th>Participant’s ID</th>
<th>Date of Withdrawal/ Dropout</th>
<th>Reason(s) of Withdrawal/ Dropout</th>
<th>Proper Unprocessed Data Withdrawn and Destroyed</th>
<th>Signature of the Investigator</th>
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</table>
Appendix 14 Chinese Medicine Syndrome Identification for AE

Instructions:
This form should be completed by a trial investigator with consultation of the participant or his/her guardian on the screening stage of the trial. Please tick one column for relevant symptom(s) or sign(s).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Symptoms and Signs</th>
<th>Associate Symptoms and Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Deficiency with wind &amp; Dryness</td>
<td>Dryness and thickening of the skin</td>
<td>Abdominal bloating after eating</td>
</tr>
<tr>
<td></td>
<td>Itchiness with excoriation and blood crusts</td>
<td>Constipations or loose stools</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pale and flabby tongue body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>White tongue coating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slippery pulse</td>
</tr>
<tr>
<td>Retention of wind &amp; dampness on the skin</td>
<td>Redness on the skin</td>
<td>Low energy</td>
</tr>
<tr>
<td></td>
<td>Severe itchiness</td>
<td>Loose stools</td>
</tr>
<tr>
<td></td>
<td>Scratches with erosion and ooze</td>
<td>Pale tongue body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thin, greasy tongue coating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wiry and slippery pulse</td>
</tr>
</tbody>
</table>

Registered Chinese medicine practitioner’s signature: ____________________

* This form was modified and translated from “Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in TCM (ZY/T001.8-94)” published by the State Administration of TCM, P. R. of China, 1994
Appendix 15  Instructions for Completing Case Report Forms

•  **Pen:**

  Always use a black ball-point pen when writing in case report forms.

•  **Text:**

  Please write clearly in legible English.

•  **Identification of participant:**

  Please ensure that the participant number & initials are clearly stated on the designated portion of each page.

•  **Missing/unavailable data:**

  Please do not leave data boxes empty. If data is missing, put a single line through the blank section and add a comment stating why the data was not available eg "not done"

•  **Abnormal data:**

  Please give the reason for any abnormal data in the space provided in the CRF.

•  **Corrections:**

  Please do not make changes with correction fluid. Draw a single line through the incorrect value so that it is still legible. Write the correct value clearly as near as possible to the original value. Initial and date the change.

•  **Dates:**

  Please write dates using this order: day, month, and year.

•  **Times:**

  Please document times using 24-hour notation.
Appendix 16  
Assessment Form for Objective Score of 
SCORAD*

Instructions: 
This form should be completed by a trial investigator with consultation of the participant or his/her guardian on the stages of screening, treatment, endpoint and following up at a minimum interval of 2 weeks.

A. Extent  
Please tick the area involved and write down the sum score

1. Table for children under two years

1a. the front

<table>
<thead>
<tr>
<th></th>
<th>Anterior head</th>
<th>Left anterior arm</th>
<th>Right anterior arm</th>
<th>Anterior torso</th>
<th>Left anterior leg</th>
<th>Right anterior leg</th>
<th>Left palm</th>
<th>Right palm</th>
<th>Genital/perineum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>8.5</td>
<td>4.5</td>
<td>4.5</td>
<td>18</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1b. the back

<table>
<thead>
<tr>
<th></th>
<th>Posterior head</th>
<th>Left posterior arm</th>
<th>Right posterior arm</th>
<th>Posterior torso</th>
<th>Left posterior leg</th>
<th>Right posterior leg</th>
<th>Left hand</th>
<th>Right hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>8.5</td>
<td>4.5</td>
<td>4.5</td>
<td>18</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Table for adults

2b. the front

<table>
<thead>
<tr>
<th></th>
<th>Anterior head</th>
<th>Left anterior arm</th>
<th>Right anterior arm</th>
<th>Anterior torso</th>
<th>Left anterior leg</th>
<th>Right anterior leg</th>
<th>Genital/perineum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>18</td>
<td>9</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2b. the back

<table>
<thead>
<tr>
<th></th>
<th>Posterior head</th>
<th>Left posterior arm</th>
<th>Right posterior arm</th>
<th>Posterior torso</th>
<th>Left posterior leg</th>
<th>Right posterior leg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Intensity Please write down the sum score

<table>
<thead>
<tr>
<th>Criteria</th>
<th>0 absence</th>
<th>1 mild</th>
<th>2 moderate</th>
<th>3 severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema/darkening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema/papulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oozing/crust</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excoriation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lichenification/prurigo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dryness (is evaluated on uninvolved areas)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Objective SCORAD:

\[
A/5 + 7B/2 = /83
\]
Appendix 17  Visual Analogue Scale for Assessment of Severity of AE (Subjective SCORAD) *

Instructions:
Point 1 and 2 on this form should be completed by patient or guardian with assistance of a trial investigator. Point 3 should be a sum of scores on Point 1 and Point 2 and filled in by a trial investigator.

1. Please circle the number on the table to scale your average for the last 3 days or night in term of skin itch, 0 is no skin itch at all; 5 is moderate and 10 is very poor.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus (itch) (0 to 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Please circle the number on the table to scale your average for the last 3 days or night in term of sleep loss, 0 is no sleep loss at all; 5 is moderate and 10 is very poor.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Loss (0 to 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Subjective SCORAD (Pruritus + Sleep loss) score: 

---

Appendix 18  Infant’s Dermatitis Quality of Life Index (IDQOL) *

1. Instructions:
The aim of this table is to record how your child’s dermatitis has been. Each question concerns THE LAST WEEK ONLY. Please answer and circle every question. The form is designed for a participant under 4 years old.

<table>
<thead>
<tr>
<th>Questions</th>
<th>All the time</th>
<th>A lot</th>
<th>A little</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Over the last week, how much has your child been <strong>itching and scratching</strong>?</td>
<td>Always crying, extremely difficult</td>
<td>Very fretful</td>
<td>Slightly fretful</td>
<td>Happy</td>
</tr>
<tr>
<td>2  Over the last week, what has your child’s <strong>mood</strong> been?</td>
<td>More than 2 hrs</td>
<td>1 - 2 hrs</td>
<td>15 mins - 1 hr</td>
<td>0 - 15 mins</td>
</tr>
<tr>
<td>3  Over the last week approximately how much time to get your child off to sleep each night?</td>
<td>5 hrs or more</td>
<td>3 - 4 hrs</td>
<td>1 - 2 hrs</td>
<td>Less than 1 hour</td>
</tr>
<tr>
<td>4  Over the last week, what was the <strong>total time</strong> that your child’s <strong>sleep was disturbed</strong> on average each night?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all/None</td>
</tr>
<tr>
<td>5  Over the last week, has your child's eczema interfered with <strong>playing or swimming</strong>?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all/None</td>
</tr>
<tr>
<td>6  Over the last week, has your child’s eczema interfered with your child <strong>taking part in or enjoying other family activities</strong>?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all/None</td>
</tr>
<tr>
<td>7  Over the last week, have there been problems with your child at <strong>mealtimes</strong> because of the eczema?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all/None</td>
</tr>
<tr>
<td>8  Over the last week, have there been problems with your child caused by the <strong>treatment</strong>?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all/None</td>
</tr>
<tr>
<td>9  Over the last week, has your child’s eczema meant that <strong>dressing and undressing</strong> the child has been <strong>uncomfortable</strong>?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all/None</td>
</tr>
<tr>
<td>10 Over the last week how much has your child having eczema been a problem at <strong>bathtime</strong>?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all/None</td>
</tr>
</tbody>
</table>

* IDQOL was adapted and modified from Lewis-Jones, M. S., Finlay, A. Y., & Dykes, P. J. (2001). The infants’ dermatitis quality of life index. *British Journal of Dermatology* (144), 104-110 with permission of the authors for research purpose.
Please check that you have answered EVERY question. Thank you.

**IDQOL score:**

2. **Scoring:**

**Questions 1 and 5-10**

<table>
<thead>
<tr>
<th>All the time</th>
<th>scored 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A lot</td>
<td>scored 2</td>
</tr>
<tr>
<td>A little</td>
<td>scored 1</td>
</tr>
<tr>
<td>None</td>
<td>scored 0</td>
</tr>
</tbody>
</table>

**Question 2**

<table>
<thead>
<tr>
<th>Always crying etc</th>
<th>scored 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very fretful</td>
<td>scored 2</td>
</tr>
<tr>
<td>Slightly fretful</td>
<td>scored 1</td>
</tr>
<tr>
<td>Happy</td>
<td>scored 0</td>
</tr>
</tbody>
</table>

**Question 3**

<table>
<thead>
<tr>
<th>More than 2 hrs</th>
<th>scored 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 hrs</td>
<td>scored 2</td>
</tr>
<tr>
<td>15 mins-1hr</td>
<td>scored 1</td>
</tr>
<tr>
<td>0-15 mins</td>
<td>scored 0</td>
</tr>
</tbody>
</table>

**Question 4**

<table>
<thead>
<tr>
<th>5hrs or more</th>
<th>scored 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 hours</td>
<td>scored 2</td>
</tr>
<tr>
<td>1-2 hours</td>
<td>scored 1</td>
</tr>
<tr>
<td>Less than 1 hour</td>
<td>scored 0</td>
</tr>
</tbody>
</table>

**Question 5-10**

<table>
<thead>
<tr>
<th>Very much</th>
<th>scored 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A lot</td>
<td>scored 2</td>
</tr>
<tr>
<td>A little</td>
<td>scored 1</td>
</tr>
<tr>
<td>Not at all / none</td>
<td>scored 0</td>
</tr>
</tbody>
</table>

The IDQOL is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score the more quality of life is impaired.

*(Please Note: That the scores associated with the different answers on Point 2 Scoring should not be printed on the IDQOL itself, as this might cause bias).*
Appendix 19  Children's Dermatology Life Quality Index (CDLQI)*

1. Instructions:
   The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick one column for each question. The form is designed for a participant at age of 5 to 16.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Very much</th>
<th>Quite a lot</th>
<th>Only a little</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Over the last week, how <em>itchy</em>, &quot;<em>scratchy</em>&quot;, <em>sore</em> or <em>painful</em> has your skin been?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Over the last week, how <em>embarrassed</em> or <em>self conscious</em>, <em>upset</em> or <em>sad</em> have you been because of your skin?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Over the last week, how much has your skin affected your <em>friendships</em>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Over the last week, how much have you changed or worn <em>different</em> or <em>special clothes/shoes</em> because of your skin?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Over the last week, how much has your skin trouble affected <em>going out, playing, or doing hobbies</em>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Over the last week, how much have you avoided <em>swimming</em> or <em>other sports</em> because of your skin trouble?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7a If <em>school time</em> - Over the last week, how much did your skin problem affect your <em>school work</em>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7b If <em>holiday time</em> - How much over the last week, has your skin problem interfered with your enjoyment of the <em>holiday</em>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Over the last week, how much trouble have you had because of your skin with other people <em>calling you names, teasing, bullying, asking questions or avoiding you</em>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Over the last week, how much has your <em>sleep</em> been affected by your skin problem?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Over the last week, how much of a problem has the <em>treatment</em> for your skin been?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please check that you have answered EVERY question. Thank you.

CDLQI score: [ ]

*CDLQI was adapted and modified from Lewis-Jones, M. S., & Finlay, A. Y. (1995). The children's dermatology life quality index (CDLQI): initial validation and practical use. *British Journal of Dermatology, 132*(6), 942-949* with permission of the authors for research purpose.*
2. Scoring:

The scoring of each question is as follows:

<table>
<thead>
<tr>
<th></th>
<th>Scored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very much</td>
<td>3</td>
</tr>
<tr>
<td>Quite a lot</td>
<td>2</td>
</tr>
<tr>
<td>Only a little</td>
<td>1</td>
</tr>
<tr>
<td>Not at all</td>
<td>0</td>
</tr>
<tr>
<td>Question unanswered</td>
<td>0</td>
</tr>
<tr>
<td>Question 7: “Prevented school”</td>
<td>3</td>
</tr>
</tbody>
</table>

The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The CDLQI can also be expressed as a percentage of the maximum possible score of 30.

(Please Note: That the scores associated with the different answers on Point 2 Scoring should not be printed on the CDLQI itself, as this might cause bias).
**Appendix 20   Dermatology Life Quality Index (DLQI) *  

1. Instructions:  
The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick one column for each question. The form is designed for a participant at age of 17 or more.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Very much</th>
<th>A lot</th>
<th>A little</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Over the last week, how <strong>itchy, sore, painful or stinging</strong> has your skin been?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Over the last week, how <strong>embarrassed or self conscious</strong>, have you been because of your skin?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Over the last week, how much has your skin interfered with you going <strong>shopping</strong> or looking after your <strong>home or garden</strong>?</td>
<td></td>
<td></td>
<td>or Not relevant</td>
</tr>
<tr>
<td>4</td>
<td>Over the last week, how much has your skin influenced the <strong>clothes</strong> you wear?</td>
<td></td>
<td></td>
<td>or Not relevant</td>
</tr>
<tr>
<td>5</td>
<td>Over the last week, how much has your skin affected any <strong>social or leisure</strong> activities?</td>
<td></td>
<td></td>
<td>or Not relevant</td>
</tr>
<tr>
<td>6</td>
<td>Over the last week, how much have your skin made it difficult for you to do any <strong>sport</strong>?</td>
<td></td>
<td></td>
<td>or Not relevant</td>
</tr>
<tr>
<td>7a</td>
<td>Over the last week, has your skin prevented you from <strong>working or studying</strong>? Yes ☐ No ☐</td>
<td>Do not fill here</td>
<td>Do not fill here</td>
<td>Do not fill here</td>
</tr>
<tr>
<td>7b</td>
<td>If &quot;No&quot;, over the last week how much has your skin been a problem at <strong>work or studying</strong>?</td>
<td></td>
<td></td>
<td>or Not relevant</td>
</tr>
<tr>
<td>8</td>
<td>Over the last week, how much has your skin created problems with your <strong>partner</strong> or any of your <strong>close friends</strong> or <strong>relatives</strong>?</td>
<td></td>
<td></td>
<td>or Not relevant</td>
</tr>
<tr>
<td>9</td>
<td>Over the last week, how much has your skin caused any <strong>sexual difficulties</strong>?</td>
<td></td>
<td></td>
<td>or Not relevant</td>
</tr>
<tr>
<td>10</td>
<td>Over the last week, how much of a problem has the <strong>treatment</strong> for your skin been, for example by making your home messy, or by taking up time?</td>
<td></td>
<td></td>
<td>or Not relevant</td>
</tr>
</tbody>
</table>

* DLQI was adapted and modified from Finlay, A. Y., & Khan, G. K. (1994). Dermatology life quality index (DLQI)--a simple practical measure for routine clinical use. *Clinical & Experimental Dermatology* 19(3), 210-216 with permission of the authors for research purpose.
Please check that you have answered EVERY question. Thank you.

**DLQI score:**

2. **Scoring:**

The scoring of each question is as follows:

<table>
<thead>
<tr>
<th></th>
<th>scored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very much</td>
<td>3</td>
</tr>
<tr>
<td>A lot</td>
<td>2</td>
</tr>
<tr>
<td>A little</td>
<td>1</td>
</tr>
<tr>
<td>Not at all</td>
<td>0</td>
</tr>
<tr>
<td>Not relevant</td>
<td>0</td>
</tr>
<tr>
<td>Question unanswered</td>
<td>0</td>
</tr>
<tr>
<td>Question 7: &quot;prevented work or studying&quot;</td>
<td>3</td>
</tr>
</tbody>
</table>

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The DLQI can also be expressed as a percentage of the maximum possible score of 30.

*(Please Note: That the scores associated with the different answers on Point 2 Scoring should not be printed on the DLQI itself, as this might cause bias).*
Appendix 21 Daily Medical Record Sheet

This daily sheet should be recorded by the patient or his/her guardian every day when you are on the period of the trial. Please take the record sheet for evaluation next time when you re-visit the trial center.

Please circle the number on the table to scale the average of the itching and sleep loss. 0 is not at all; 5 is moderate and 10 is very severe.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching of the skin (0 – 10)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep loss (0 – 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Please circle the number on the table to scale the average intensity of the signs on your skin.

<table>
<thead>
<tr>
<th></th>
<th>0 absence</th>
<th>1 mild</th>
<th>2 moderate</th>
<th>3 severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness of the skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0 absence</th>
<th>1 mild</th>
<th>2 moderate</th>
<th>3 severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryness of the skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0 absence</th>
<th>1 mild</th>
<th>2 moderate</th>
<th>3 severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness of the skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If any adverse reaction develops, please fill in the form “Adverse Event Questionnaires” separately.

<table>
<thead>
<tr>
<th>Date &amp; Time</th>
<th>Usage of the Chinese Herbal Cream</th>
<th>Itching of The Skin (0 To 10)</th>
<th>Sleep Loss (0 To 10)</th>
<th>Redness of the Skin (0 To 10)</th>
<th>Dryness of the Skin (0 To 10)</th>
<th>Thickness of the Skin (0 To 10)</th>
<th>Application of other Medicines (Dosage &amp; Name of the Medication)</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>Participant’s Initials:</td>
<td>Participant’s ID:</td>
<td>Date: <em><strong>/</strong></em>/_____</td>
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</table>

Please add additional sheet if there is not enough space.
Appendix 22  Outcome Measures Sheet

Instruction: This form is designed for outcome measures assessed and recorded by the trial investigator.

<table>
<thead>
<tr>
<th>Participant’s ID</th>
<th>Date of Measurement</th>
<th>Subjective Sore of SCORAD (Self Rated Symptoms and Signs)</th>
<th>Objective Score of SCORAD</th>
<th>Score of QoL</th>
<th>Blood Tests Results</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 1-14</td>
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<td></td>
<td>Day 15</td>
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<td></td>
<td>Day 29</td>
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<td></td>
<td>Day 43</td>
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<td></td>
<td>Day 57</td>
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<td>Endpoint</td>
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<td></td>
<td>Day 71</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 99</td>
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<tr>
<td></td>
<td>Follow-up</td>
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</tr>
</tbody>
</table>
Appendix 23  Pathology Tests

Participant’s Last Name:  Given Name:  Sex:  Date of Birth:

Participant’s Address:

Tel: (H)  Tel: (B)  Your Ref:

Medicare Card Number:

Tests Requested:

Full blood tests  Liver function tests  Renal function tests  IgE

Pregnancy test (only if applicable)

Clinical notes:

Copy reports to:

Requesting doctor (Provider number, initials, surname, and address):

Doctor’s signature and request date:
Appendix 24  Adverse Event Questionnaires

Please record any unexpected feelings or symptoms or signs during participation of the trial on the following table and report any severe adverse event to the investigator on (03) 9925 7635 and stop using the intervention products immediately until further instruction is given.

Please scale the severity of the event by using the VAS table below and write down the score on the Record Sheet of Adverse Event. 0 is not at all, 5 is moderate and 10 is very severe.

1. VAS table

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

2. Record Sheet of Adverse Event

<table>
<thead>
<tr>
<th>Type of Event (symptoms and/or signs)</th>
<th>When was that happen? (date and time)</th>
<th>How long did it last for?</th>
<th>Severity of the event (0 to 10)</th>
<th>What action did you do for the event?</th>
</tr>
</thead>
</table>


RMIT UNIVERSITY

Traditional & Complementary Medicine Research Group, School of Health Sciences

Appendix 25  Record Sheet of the Compliance Check

<table>
<thead>
<tr>
<th>Participant’s ID</th>
<th>Visit Date &amp; Day</th>
<th>Sequential Number of the Container</th>
<th>Weight of Returned Creams</th>
<th>Investigator’s Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 43</td>
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<td></td>
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<tr>
<td></td>
<td>Day 57</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Day 71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 99 Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>