Ear-acupressure for allergic rhinitis

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Discipline of Chinese Medicine
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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 quality 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.

Shuiqing Zhang

Date
To my dearest father and mother  
with deepest gratitude and love

献给我亲爱的父亲张广明和母亲夏秀萍
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Publications

Journal articles


Conference papers


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<tbody>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>ANZCTR</td>
<td>the Australian New Zealand Clinical Trial Registry</td>
</tr>
<tr>
<td>AR</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>ARIA</td>
<td>Allergic Rhinitis and its Impact on Asthma</td>
</tr>
<tr>
<td>ASCIA</td>
<td>Australasian Society of Clinical Immunology and Allergy</td>
</tr>
<tr>
<td>BSACI</td>
<td>British Society for Allergy and Clinical Immunology</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary and alternative medicine</td>
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<tr>
<td>CHM</td>
<td>Chinese herbal medicine</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
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<td>ENT</td>
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<td>GM-CSF</td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamus-pituitary-adrenal</td>
</tr>
<tr>
<td>IAR</td>
<td>Intermittent allergic rhinitis</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>ISAAC</td>
<td>the International Study of Asthma and Allergies in Childhood</td>
</tr>
<tr>
<td>MD</td>
<td>Mean difference</td>
</tr>
<tr>
<td>MiniRQLQ</td>
<td>Mini Rhinoconjunctivitis Quality of Life Questionnaire</td>
</tr>
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<tr>
<td>SR</td>
<td>Systematic review</td>
</tr>
<tr>
<td>STAI</td>
<td>State-Trait Anxiety Inventory</td>
</tr>
<tr>
<td>TGA</td>
<td>the Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>TNSS</td>
<td>Total nasal symptom score</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Summary

Allergic rhinitis (AR) is a common respiratory allergic condition characterised by sneezing, itching, rhinorrhoea and/or nasal congestion, affecting 16% of the Australian population. Although it is not a life threatening disease, it has a significant impact on patients’ quality of life in terms of physical, psychological and social aspects. There is also a substantial economic burden on sufferers and the health care system associated with AR.

Current Western medical management of AR includes pharmacotherapy, allergen-specific immunotherapy and others. These therapies usually do not completely relieve all AR symptoms, with some unwanted side effects. Chinese medicine, including acupuncture and Chinese herbal medicine (CHM), has a long history of treating AR in China. Ear-acupressure is a subtype of acupuncture. Previous clinical studies suggested that ear-acupressure was effective and safe for AR management. However, there was insufficient evidence to confirm the claims of clinical efficacy for ear-acupressure in AR. The aim of this study was to investigate the efficacy and safety of ear-acupressure for the clinical management of AR by conducting systematic reviews and randomised controlled trials (RCTs). The study consists of two systematic reviews, two pilot RCTs and one main RCT:

**Systematic review 1: Ear-acupuncture/ear-acupressure for AR**

This systematic review was conducted prior to designing the clinical trial protocol. By systematically reviewing previous RCTs on ear-acupuncture/ear-acupressure for AR, it was concluded that ear-acupressure might be effective and safe for AR. However, the previous RCTs in this area suffered methodological weakness and a rigorously designed RCT was required (Appendix A4.2, publication 2).
Systematic review 2: Sham control methods in ear-acupuncture/ear-acupressure RCTs

In order to determine the sham control method for the RCT, a systematic review on all previous ear-acupuncture/ear-acupressure RCTs was conducted. There were four types of control methods that had been used in previous ear-acupuncture/ear-acupressure RCTs:

- Type I: non-specific ear points for the condition treated;
- Type II: non-ear points;
- Type III: placebo needles or adhesive patches; and
- Type IV: pseudo-interventions

Among these four types of sham control methods, type I method (non-specific ear points) was the most commonly used sham/placebo control. Based on the findings of this systematic review, type I sham control was employed in RCTs.

Ear-acupressure for AR RCT: Pilot study I (feasibility study)

The trial protocol and ethics application were finalised and approved in November 2007. In order to assess the feasibility of the trial protocol, a pilot study was conducted between May and November 2008 at RMIT University’s Bundoora campus. Eighteen (18) perennial allergic rhinitis (PAR) participants were included in this pilot study with 17 of them completed the pilot trial. No serious adverse event was reported.

It was demonstrated that ear-acupressure as an intervention could be effectively employed in a trial setting including participants recruitment, initial assessment, delivery of treatment and data collection. The pilot study also identified several areas
of improvement which were incorporated into the amended trial protocol that was submitted to and approved by the RMIT Human Research Ethics Committee in August 2008.

**Ear-acupressure for AR RCT: Pilot study II (efficacy study)**

Pilot study II (efficacy study) was conducted between September and December 2008 to investigate the efficacy of ear-acupressure for seasonal allergic rhinitis (SAR) and to provide data for sample size estimation for the main trial. Sixty-three (63) SAR participants were included in this pilot, of whom 57 completed the study. At the end of the eight-week treatment period, significant differences between the two groups were found in terms of sneezing, total nasal symptoms, global nasal and non-nasal symptoms and regular activities at home and work. No severe adverse event was reported (Appendix A4.3, publication 3). Based on the findings of this study, the sample size of the main trial was calculated using G. Power 3.0.5 Software. It was estimated that the main trial requires 116 participants in each group and 232 in total.

**Ear-acupressure for AR RCT: the main trial**

The ear-acupressure for the AR main trial was conducted in 2009 and 2010 according to the amended protocol, at two trial centres: Melbourne, Australia and Guangzhou, China. This PhD project was to investigate the efficacy and safety of ear-acupressure for allergic rhinitis at the Australia centre of the multi-centre trial. Therefore, only the results from Australian trial centre (n=117) are reported in this thesis. Data from the other Centre will be handled separately, but may be combined in publications. The trial lasted for 22 weeks including a two-week run-in period, an eight-week treatment period and a 12-week follow-up period. Assessment of the treatment outcomes included symptom severity scores using a four point scale,
seven-point visual analogue scale (VAS) and a quality-of-life questionnaire, relief medication scores, and patients’ opinion during the run-in period, treatment and follow-up period. Significant differences between two groups were found in the following items: total nasal symptom, sneezing, blocked nose, itchy nose, watery eyes, global nasal and non-nasal symptoms, global quality of life, activity and sleep domain at the end of treatment period; and total nasal symptoms, blocked nose symptom and sleep domain at the end of follow-up period. Some mild and moderate discomforts were reported by participants during the treatment period. However, these discomforts were short-term and effectively managed by refinement of the pressing techniques by participants. No medical treatment was required for the management of these events.

Findings from this main trial suggested that ear-acupressure is effective and safe for symptomatic control and quality of life improvement in AR.

**Conclusion**

This thesis presents outcomes of two systematic reviews that address key research questions concerning the methodology and current state of evidence of ear-acupressure for AR, followed by findings from two trials that determine the efficacy and safety of ear-acupressure for AR. This is the first comprehensive examination of the potential role of a semi-self-administered traditional medicine technique in the management of a highly prevalent clinical condition. Further evaluation in different population is needed, and particularly, cost-effectiveness analysis is required to determine the value for money in the healthcare system that will facilitate further translation of clinical evidence into practice.
Chapter 1: General Introduction

1.1 Background

AR was initially described in 1929 as “the three cardinal symptoms in nasal reactions occurring in allergy are sneezing, nasal obstruction and mucous discharge” (Hansel, 1929). Currently, the definition of AR is “a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation” (Bousquet, Khaltaev, et al., 2008). It is an immune response triggered by nasal membrane exposure to specific allergens such as pollens, moulds, animal dander and dust mites. The main symptoms of AR are nasal symptoms such as sneezing, itching, rhinorrhoea and/or nasal congestion. These symptoms are provoked by a complicated network involving mediators, cytokines, chemokines, neuropeptides, adhesion molecules and cells.

AR is a major chronic respiratory disease due to its high prevalence and significant impact on patients’ quality of life. The prevalence of AR is high worldwide and it has been increasing in the last decades (Bousquet, Khaltaev, et al., 2008). The increase in prevalence may be caused by the change in people’s life style, the environment and the weather. In Australia, AR is one of the most common long-term conditions and it affects approximately 16% of the Australian population (Australian Institute of Health and Welfare (AIHW), 2006). The prevalence of AR in the Melbourne area is also reported as very high due to the local botanical environment (Bousquet, Leynaert, et al., 2008).

Although AR symptoms are reversible spontaneously with reduction of allergen exposure or can be controlled under proper treatment, they significantly impact on
patients’ quality of life through causing sleep disturbance, learning disability or work impairment (Juniper, 2001). In addition, AR is considered a risk factor for asthma, sinusitis and other co-morbidities such as conjunctivitis. Therefore, AR leads to a substantial burden on health and the economy (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

The current conventional medical managements of AR include allergen avoidance, pharmacotherapy and immunotherapy. However, these treatments have limitations. Firstly, the inhalant allergens such as pollens, moulds, animal dander and dust mites exist in the air. For AR sufferers, to totally avoid those allergens is not feasible. Secondly, the current pharmacologic managements for AR usually do not provide complete symptomatic relief and often cause unwanted side effects. For example, anti-histamines are the most commonly prescribed medications for AR as histamine is the major mediator involved in the pathophysiology of allergic symptoms. The first generation of anti-histamine medications had severe central nervous system side effects. Although the second generation of anti-histamine medications avoid the central nervous system side effects, other side effects have been reported (such as cardiac side effects). Another type of drug prescribed for AR is the glucocorticosteroids due to their anti-inflammatory and other effects. Local and systemic side effects caused by glucocorticosteroids are also commonly reported. Thirdly, specific immunotherapy may cause serious adverse events such as systemic allergic reactions. Due to the side effects or the inability to completely relieve all symptoms for all patients of the conventional medical approaches, there has been an increasing trend among AR sufferers towards seeking complementary and alternative medicine (CAM) treatments for AR (Schafer, Riehle, Wichmann, & Ring 2002; Xue, Thien, Zhang, Da Costa, & Li, 2003; Xue et al., 2007).
The use of CAM has been increasing in recent years in the Western countries (Eisenberg et al., 1998; Eisenberg et al., 1993; Ramsay, Walker, & Alexander, 1999; Thomas, Nicholl, & Coleman, 2001). In Australia, more than two-thirds of the population used CAM therapies (68.9%) (Xue, Zhang, Lin, Da Costa, & Story, 2007). Chinese medicine, including Chinese herbal medicine (CHM) and acupuncture therapy, is considered a part of CAM. It has also been used in China for a great variety of conditions for thousands of years. In the Western countries, CHM and acupuncture are also commonly used. The philosophy of Chinese medicine is to restore balance of the human body and thus overcome the disease. Recently, clinical researchers have provided quality data concerning the efficacy and safety of CHM for AR (Chui, Shek, Fong, Szeto, & Chan, 2010; Matkovic et al., 2010; Xue, Thien, Zhang, Da Costa, & Li, 2003) and acupuncture for AR (Magnusson, Svensson, Leirvik, & Gunnarsson, 2004; Ng et al., 2004; Xue et al., 2007). Based on the reported evidence of acupuncture for AR, needling process with skin penetration is a hurdle for wider acceptance of acupuncture in the AR population. Therefore, a non-invasive ear-acupressure technique would be advantageous for AR sufferers, however, data on its benefit and safety is lacking.

Ear-acupuncture/ear-acupressure is an alternative form of the traditional body acupuncture. It originated in ancient China and was further developed in France in the 1950’s. It views the ear as a microcosm of the body in which each part of the body is projected on the ear (Frank & Soliman, 2006). Instead of stimulating the acupoints on the body, ear-acupuncture/ear-acupressure stimulates acupoints on the ears. To generate stimulation on the ear acupoints, ear-acupuncture with needle insertion or ear-acupressure using ear-pellets attached to ear acupoints are both
commonly used in clinical practice. These methods have a long history of clinical practice in the Western world and China for a range of conditions. Generally speaking, ear-acupressure is safer compared with needling as it does not involve skin penetration (Frank & Soliman, 2006). Furthermore, when applying the treatment of ear-acupressure by attaching pellets or seeds to ear points, patients are requested to periodically press the pellets themselves. Therefore, patients are also involved in the administration of the treatment and the stimulation intensity on the ear points is controlled by the patients, not the practitioner alone.

As a microsystem, each part of the whole body has a corresponding location on the ear, so there are ear points that relate to the nose, the eyes and also to allergy. Stimulating these points aims to produce therapeutic effects on AR symptoms. In recent years, researchers have conducted clinical trials on ear-acupressure/ear-acupuncture for AR to investigate the efficacy and safety of these methods (Gao, Liu, & Zhou, 2008; Qi & Wang, 2008; Rao & Han, 2006; Ye, Luo & Xia, 2008). All these clinical studies have provided positive results. However, at the commencement of this study there was not, as yet, any systematic review to assess the current evidence in this area.

Therefore, we conducted this study to determine clinical evidence for the efficacy and safety of ear-acupressure for AR.

1.2 Study design

Randomised controlled trials (RCTs) are considered powerful tools in clinical research for testing the efficacy and safety of healthcare services since they can
separate the “specific” from the “unspecific” or “placebo” effects of an intervention (Dincer & Linde, 2003). This study is designed as an RCT to evaluate the efficacy and safety of ear-acupressure for AR.

Prior to designing the trial protocol, it was considered important to conduct a systematic review to evaluate all currently available RCTs on this topic. The aim of this review was to provide evidence for the design of the ear-acupressure for AR RCT. This review followed the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (Higgins & Green, 2006). All types of ear-acupuncture/ear-acupressure for all types of AR RCTs were included in the systematic review. The findings from this review provided evidence on the effectiveness and safety of these interventions as well as data that informed the design of the RCTs of ear-acupressure for AR discussed below.

For designing a RCT, if the intervention is a physical procedure, the placebo control is not possible to be an inert one. In this case, sham control methods will be employed. Hence, the question arises: how to design an appropriate sham control for an ear-acupressure RCT? In order to develop a well-designed RCT on ear-acupressure, another systematic review focusing on all the sham control methods used in previous ear-acupuncture/ear-acupressure studies was undertaken. This review also followed the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (Higgins & Green, 2006). All the available sham controlled RCTs of any type of ear-acupuncture or ear-acupressure for any type of clinical conditions were included in this review.
Based on the findings from above two systematic reviews, the protocol of a randomised, single-blinded, sham controlled clinical trial on ear-acupressure for AR was finalised.

In order to test the feasibility of the trial protocol, a small sized pilot study (Pilot study I (feasibility study)) was conducted in 2008. As a result of completing this pilot study, some minor methodological weaknesses were found. Consequently, amendments were made to the protocol for the main RCT. Furthermore, due to the lack of reliable data for sample size calculation for the main trial, Pilot study II (efficacy study) was conducted in 2008. The effect size in this pilot study was used for sample size calculation for the main trial.

The main trial was an international, multi-centre, adequately powered, randomised, single-blinded, sham controlled clinical trial. It was conducted at two trial centres: one in Australia and one in China, between 2009 and 2010. The results from Australian centre are reported in this thesis.

The main structure of this study is shown in Figure 1:
Figure 1: Structure of ear-acupressure for AR study
1.3 Aims and Objectives

The aims of the study were to investigate whether ear-acupuncture/ear-acupressure treatment may provide effective symptomatic relief for AR and whether ear-acupuncture/ear-acupressure treatment is safe in the management of AR, by conducting two systematic reviews and a rigorously-designed RCT.

The objectives of two systematic reviews are:

a. To evaluate whether ear-acupuncture/ear-acupressure is effective for the management of AR according to currently available studies;
b. To evaluate whether ear-acupuncture/ear-acupressure is safe for the management of AR according to current available RCTs;
c. To summarise the designs of sham control methods from currently available ear-acupuncture/ear-acupressure RCTs.

The objectives of the RCTs are:

a. To evaluate whether ear-acupressure can relieve AR symptoms, including nasal symptoms, non-nasal symptoms and global nasal and non-nasal symptoms;
b. To test whether ear-acupressure can improve AR sufferers’ quality of life;
c. To assess whether ear-acupressure can reduce AR medication usage; and
d. To investigate whether ear-acupressure is a safe treatment for the AR management.

The hypotheses tested in the RCTs are:

a. Null hypothesis:
There was no statistically significant difference at post treatment between the intervention and control groups.

b. Alternative hypothesis:
There was a statistically significant difference at post treatment between the intervention and control groups.

1.4 Location of the study

The main trial was an international, multi-centre, clinical trial conducted at two clinical trial centres:

- Australian centre
  The Australian centre is in the Discipline of Chinese Medicine, School of Health Sciences, RMIT University, Victoria, Australia.

- China centre
  The centre in China is located in Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, China.

Prior to the commencement of the main trial, the two systematic reviews and two pilot studies were conducted at the Australian centre only.

This thesis only reports the findings from the Australian centre, in addition to two systematic reviews, and two pilot studies.

1.5 Organisation of the thesis

This thesis consists of nine chapters, as follows:
• Chapter 1 briefly introduces the background of AR and ear-acupressure, and the aims and objectives of this study. The study structure and the organisation of the thesis are also introduced in this chapter.

• Chapter 2 provides a descriptive review, from the Western medicine perspective, on AR with respect to its definition, epidemiology, classification, diagnosis and clinical management.

• Chapter 3 addresses AR from Chinese medicine point of view. It explains the Chinese medicine managements including CHM and acupuncture for AR, as well as the current clinical research in this area.

• Chapter 4 introduces ear-acupuncture/ear-acupressure treatment methods, systematically reviews the current research on ear-acupuncture/ear-acupressure for AR, and the sham control designs used in all ear-acupuncture/ear-acupressure sham-controlled RCTs.

• Chapter 5 presents the details of the methodology of the RCT including recruitment, selection criteria, trial procedures, outcome measures, data collection and data analysis.

• Chapter 6 reports the procedure and results of Pilot study I (feasibility study). Upon the completion of this pilot study, some minor changes in the trial methods were made for the further trials.

• Chapter 7 reports the procedure and results of Pilot study II (efficacy study). The sample size of the main trial was calculated based on the results of this pilot study.

• Chapter 8 reports the procedure and results of the ear acupressure for the AR main trial conducted at the Australian centre.
Finally, Chapter 9 discusses the strengths and limitations of the whole project, outlines the overall evidence and provides recommendations for future research on ear-acupressure for AR and the implications for clinical practice.
Chapter 2: Literature review on allergic rhinitis from the Western medicine perspective

This chapter provides a review, from the Western medicine perspective, of allergic rhinitis (AR) with respect to its definition, epidemiology, classification, diagnosis and clinical management. The drawbacks of current mainstream treatments for AR are elaborated to address the need to seek additional approaches to AR management.

Rhinitis, characterised mainly by nasal symptoms, is a condition of irritation and inflammation of the nose lining. Due to its different causes, rhinitis is classified as: infectious rhinitis, AR, occupational rhinitis, drug-induced rhinitis, hormonal rhinitis and others (Bousquet, Khaltaev, et al., 2008; Bousquet, Van Cauwenberge, & Khaltaev, 2001). Among them, AR is the most common non-infectious rhinitis.

AR is a major chronic respiratory disease due to its high prevalence, impact on quality of life, impact on work/school performance and productivity, significant economic burden (Juniper et al., 2005) and its links with asthma (Scadding, 2008).

2.1 Definition of AR

AR, commonly called “hay fever”, is a disorder induced by inflammation of the nasal membranes. Exposure to specific allergens such as pollens, moulds, animal dander and dust mites leads to an IgE-mediated immune response and induces inflammation of the nose lining. Clinically, AR is defined as a “symptomatic disorder of the nose induced after allergen exposure by the IgE-mediated inflammation” (Bousquet, Khaltaev, et al., 2008).
AR is characterised by one or more nasal symptoms including sneezing, itching, rhinorrhoea and/or nasal congestion. In addition, AR nasal symptoms are frequently accompanied by symptoms involving the eyes, ears and throat, such as itchy and watery eyes, redness and tearing of the eyes, ear fullness and popping, itchy throat, post nasal drip, chronic cough, and feeling of pressure over the cheeks and forehead. Malaise, weakness and fatigue may also be present in AR sufferers (Dykewicz et al., 1998; Skoner, 2001).

2.2 Epidemiology of AR

2.2.1 Prevalence in global general population

AR has a high prevalence at 10% to 45% globally. The results of recent prevalence studies in a number of countries are summarised in Table 1.
# Table 1: Prevalence of AR in specific countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence of AR</th>
<th>Reference</th>
<th>Country</th>
<th>Prevalence of AR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>16.1%</td>
<td>(ABS, 2006)</td>
<td>Japan</td>
<td>44.2%</td>
<td>(Sakashita et al., 2009)</td>
</tr>
<tr>
<td>Belgium</td>
<td>28.5%</td>
<td>(Bauchau &amp; Durham, 2004)</td>
<td>Lebanon</td>
<td>38.6%</td>
<td>(Musharrafieh et al., 2009)</td>
</tr>
<tr>
<td>France</td>
<td>24.5%</td>
<td>(Bauchau &amp; Durham, 2004)</td>
<td>Poland</td>
<td>22.54%</td>
<td>(Samolinski et al., 2009)</td>
</tr>
<tr>
<td>Germany</td>
<td>20.6%</td>
<td>(Bauchau &amp; Durham, 2004)</td>
<td>Spain</td>
<td>21.5%</td>
<td>(Bauchau &amp; Durham, 2004)</td>
</tr>
<tr>
<td>Gulf Arab population</td>
<td>32%</td>
<td>(Alsowaidi, Abdulle, Shehab, Zuberbier, &amp; Bernsen, 2010)</td>
<td>Turkey</td>
<td>23.1%</td>
<td>(Cingi et al., 2009)</td>
</tr>
<tr>
<td>Italy</td>
<td>16.9%</td>
<td>(Bauchau &amp; Durham, 2004)</td>
<td>UK</td>
<td>26%</td>
<td>(Bauchau &amp; Durham, 2004)</td>
</tr>
</tbody>
</table>

Using a conservative estimate, it is suggested that AR occurs in approximately 500 million people in the world (Bousquet, Khaltaev, et al., 2008). The relative proportions of AR sufferers in different areas are shown in Figure 2.
Figure 2: Worldwide AR prevalence

Among all the areas, the Asia-Pacific area has the highest AR population (over 150 million people) (Bousquet, Khaltaev, et al., 2008).

2.2.2 Increase of AR prevalence

A trend of increase in AR prevalence has been observed in the last few decades (Demir et al., 2005; Galassi et al., 2006; Latvala, von Hertzen, Lindholm, & Haahtela, 2005; Linneberg et al., 1999; Verlato et al., 2003).

To estimate the change in AR prevalence, the largest collaborative epidemiological study - the International Study of Asthma and Allergies in Childhood (ISAAC) was carried out in about 50 countries. The Phase I study took place between 1992 and 1998, and the Phase III study repeated the survey five years later to assess the
trends in prevalence. Comparing the results from Phase I and Phase III of this study, it was found that there was a global increase in AR prevalence in the 6 to 7 years age group and in the 13 to 14 years group across most countries (Asher et al., 2006; Bousquet, Khaltaev, et al., 2008).

2.2.3 AR prevalence in Australia and China

In Australia, the AR prevalence in the total population has increased from 13.9% in 1995 to 16.1% in 2004-05 (ABS, 2006; Australian Institute of Health and Welfare (AIHW), 2006) with a per annum increase of 0.22% (Australasian Society of Clinical Immunology and Allergy (ASCIA), 2007). The National Health Survey conducted in 2002 reported that there were 2.9 million people suffering from AR (Australian Institute of Health and Welfare (AIHW), 2005), while in 2007 there were in total 3,342,870 Australian AR sufferers of all ages including 15.6% of the total male population (1,613,432) and 16.6% of the female population (1,729,438) (Australasian Society of Clinical Immunology and Allergy (ASCIA), 2007). Considering the growth of population and the trend of increasing prevalence, it is estimated that there will be 7.86 million AR sufferers in Australia by 2050 (Australasian Society of Clinical Immunology and Allergy (ASCIA), 2007). The results of the ISAAC study proved that in Australia, the prevalence of AR among children aged 6-7 years old has increased from 9.8% to 12.9% from 1994-5 to 2001-3 (Asher et al. 2006).

The prevalence of AR in Australia varies by region. According to a self-reported survey in 2001, the Australian Capital Territory had the highest prevalence of AR (25.3%) whilst the lowest AR prevalence was found in New South Wales (13.1%) (Public and Environmental Health Service, 2003) (Figure 3).
ACT: Australian Capital Territory; SA: South Australia; WA: Western Australia; VIC: Victoria; Qld: Queensland; NSW: New South Wales; Aust: Australia. (Public and Environmental Health Service, 2003)

**Figure 3: Variations of AR prevalence in Australian states and territory**

Based on participants' report, the AR prevalence in the Melbourne area is also reported to be high – 46% of nasal allergy (responded positively to the question “Do you have hay fever or nasal allergies”), and 31.8% of atopic (inherited allergic condition) nasal allergy (responded positively to the question and also having a positive response to skin tests) (Bousquet, Leynaert, et al., 2008). A study indicated that 19.8% of school children were AR sufferers in 2002 in Melbourne (Robertson, Roberts, & Kappers, 2004).

The prevalence of AR in China is also high and has been increasing in recent years. According to the ISAAC Phase I and Phase III study, the prevalence of AR among 13-14 age group children in China was reported to be 8.1% in Phase I period (1994-1995), while 10.4% in Phase III period (2004-2005) with an annual increase of 0.33%
(Asher et al., 2006; Bousquet, Khaltaev, et al., 2008). Another survey conducted between December 2009 and January 2010 in Asia-Pacific area (Allergies In Asia-Pacific: A Landmark Survey of Nasal Allergy Sufferers (AIAP)) concluded that 9% of the population in China had been diagnosed with nasal allergies, which is equal to the average AR prevalence of the entire Asia-Pacific area.

### 2.2.4 Factors impacting on AR prevalence

The factors which cause variation in AR prevalence may differ from one location to another and from one age-group to another. They can be related to aspects of lifestyle, dietary habits, microbial exposure, economic status, indoor or outdoor environment, climatic variation, awareness of the disease and the management of symptoms (Asher et al., 2006).

Firstly, the geographic factors cause differences in the AR prevalence. For example, in Western and developed countries such as the United States, Australia, New Zealand and United Kingdom, the prevalence of AR is higher than that in developing countries. These differences may not be simply caused by the difference between ethnic groups. In fact, whether genetic, environmental, socio-economic or cultural factors contributed to this difference is yet to be confirmed (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

Secondly, the life style differences between rural and urban areas may have an impact on the AR prevalence. Studies have shown that AR prevalence is higher in urban than in rural areas (Gergen & Turkeltaub, 1992; Nicolaou, Siddique, & Custovic, 2005; Soto-Quiros, Silverman, Hanson, Weiss, & Celedon, 2002). This difference may be caused by the fact that the pollen counts differ in urban and rural
areas or the countryside lifestyle could possibly protect children from the allergy development (Kilpelainen, Terho, Helenius, & Koskenvuo, 2002; Leynaert et al., 2001; Riikjarv, Annus, Braback, Rahu, & Bjorksten, 2000; Wickens et al., 2002). Therefore, adoption of an urbanised “Western” lifestyle such as having indoor animals, sharing a bedroom with a smoker, poor house ventilation and exposure to motor vehicles may lead to an increase the AR prevalence in developing countries (Gerez, Lee, van Bever, & Shek, 2010; Yemaneberhan et al., 1997).

Thirdly, age also influences the AR prevalence. There is a significant variation in the prevalence of AR among different age groups. Although AR may occur in persons of all ages, it peaks between the ages of 6 and 20 (Bellanti & Wallerstedt, 2000). That is, the onset of AR is more common in childhood, adolescence and early adult years. On average, 40% of AR patients experience AR symptoms between 8 and 11 years of age, and up to 80% of AR patients experience symptoms by the age of 20 (Skoner, 2001).

In addition, there are other factors that relate to increases in AR prevalence, such as traffic-related air pollution which may play a role in the high prevalence in urban areas (Lindgren et al., 2009). Global climate change may also have an impact on the increasing AR prevalence due to the growth of atmospheric carbon dioxide (Beggs & Bambrick, 2005). Also, higher temperatures may expand the pollen quantity and induce longer pollen seasons (Sheffield, Weinberger, & Kinney, 2011; Ziska et al., 2011).
2.3 Mechanisms of AR

AR is a disease of nasal membrane inflammation mediated by IgE after allergen exposure. Symptoms of AR are provoked by a complicated network involving mediators, cytokines, chemokines, neuropeptides, adhesion molecules and cells. Understanding the mechanisms of the complex inflammatory reactions of AR provides a framework for rational therapy. This section introduces the pathophysiology of AR and the mechanisms of nasal inflammation resulting from an IgE mediated allergy.

Briefly, when the nasal mucosa is exposed to a very small quantity of allergens, the antigens are phagocytosed by antigen presenting cells in the mucosal epithelium. The antigen presenting cells process and break antigens down into peptide fragments which bind to the antigen recognition sites of major histocompatibility complex class II molecules (Baraniuk, 1997). This membrane-bound complex is now presented to T cell antigen specific receptors. In an allergic person, the antigen-specific T-cell receptors of Th$_0$ cells recognise the antigenic peptides and differentiate into Th$_2$ lymphocytes. Th$_2$ cells release their characteristic combination of cytokines, which activate B cells to form IgE-secreting plasma cells. The IgE molecules bind to high affinity IgE-specific Fc-receptors on the membrane of mast cells and basophils (Mygind, 1996). With later exposure to the same allergen, the cross-link of bound IgE causes cell degranulation and triggers the release of various inflammatory mediators (Kuby, 1997) which is a critical event in acute AR. Histamine, tryptase, prostaglandin and bradykinin are rapidly released during this immediate allergic (Baraniuk, 1997) causing sneezing, nasal itch and rhinorrhoea. The late phase response usually occurs four to twelve hours after the immediate response during which there is a large increase of eosinophils, basophils and other leukocytes in response to
chemoattractants. Histamine and leukotrienes are likely to be released from basophils rather than mast cells because tryptase remains unchanged. It is believed that other cytokines such as IL-5, IL-6, and IL-1 are also released from the new infiltration granulocytes and granulocyte-macrophage colony-stimulating factor (GM-CSF), which may be released from leukocytes and epithelium. The repetition of this process may lead to chronic inflammation (Baraniuk, 1997) (Figure 4).

(Adapted from “Current state of clinical research on Western medicine for allergy” (Thien, 2003))

**Figure 4: Pathogenesis of allergy**

The following sections, 2.3.1 to 2.3.5, explain in detail the mechanisms of nasal inflammation caused by an IgE mediated allergy and the course of nasal challenge developing to chronic rhinitis.
2.3.1 Nasal mucosa

Firstly, understanding the structure of the nasal mucosa helps with understanding the nasal symptoms caused by inflammation. Inside the nose, there is a bony framework covered with mucosa which consists of three layers. There is also a thin layer of mucus on the surface of the nasal mucosa. Being an unspecific protection against infection, nasal fluid consists of the secretions produced by the submucosal gland and goblet cells, derived from the eyes or from the paranasal sinuses (Mygind et al., 1987). In rhinitis, the hypersecretion from nasal mucous glands is important because an active secretory process in the nose appears to be the main cause of watery rhinorrhoea (Brofeldt, Mygind, Sorensen, Readman, & Marriott, 1986).

Allergic inflammation can also decrease the mucociliary clearance function of the ciliated epithelium. The nasal mucosa has a high degree of vascularisation. The arteries in the nose microvasculature are surrounded by a smooth muscle layer which controls the blood supply. The nasal mucosa can expand or shrink rapidly by changing the blood volume (Holmberg, Bake, & Pipkorn, 1988). Therefore, the capacitance vessels or sinuses can be distended to block the nasal lumen or be emptied to open the nasal passages (Holmberg, Bake, & Pipkorn, 1988).

2.3.2 Nasal inflammation

In the nasal inflammation caused by an IgE-mediated allergy reaction, cells, mediators, cytokines, chemokines and adhesion molecules all cooperate in a complex network provoking specific symptoms and nonspecific nasal hyperreactivity (Bousquet, Khaltaev, et al., 2008).
Mast cells release histamine and granule protein, arachidonic acid metabolites and cytokines (Bradding et al., 1993). Therefore, mast cells play an important role in immediate-phase allergic response, late-phase response and ongoing allergic inflammation (Bousquet, Van Cauwenberge, & Khaltaev, 2001). Basophils and eosinophils also release cytokines during allergic reaction. Other cells such as T-lymphocytes, B-lymphocytes, macrophages, dendritic cells, epithelial cells, endothelial cells and fibroblasts are all involved in allergic reactions (Costa, Weller, & Galli, 1997; Foresi et al., 1997; Naclerio, 1997).

Histamine has been recognised as the main mediator in allergic disorders since the 1920s (Bachert, 1998). Histamine is quantitatively the major mediator released after the IgE activation on mast cells and basophils. It can cause many AR symptoms such as rhinorrhea, sneezing, itchiness and nasal obstruction (Bachert, 1998; Beaven, 1978; Corrado, Gould, Kassab, & Davies, 1986) through its effects on sensory nerves, glands or vessels and its pro-inflammatory effects. Other mediators such as the Arachidonic acid metabolic pathway and the Kinins system are also considered to have effects on AR (Naclerio, 1997).

Pro-inflammatory cytokines such as IL-1, tumour necrosis factor (TNF), IL-6 and IL-18 are multifunctional unspecific enhancers of inflammation; while Th2-cytokines such as IL-4 and IL-3 are important in the regulation of IgE; and IL-3, GM-CSF and IL-5 are related to the production of eosinophils. Chemokines are a family of small cytokines or proteins secreted by cells. The major role of chemokines in AR is to act as a chemoattractant to guide the migration of cells (Bousquet, Van Cauwenberge, & Khaltaev, 2001).
Cellular adhesion molecules are an essential part in binding circulating leukocytes to the vascular endothelium at sites of inflammation (Baroody, Lee, Lim, & Bochner, 1995).

In short, the nasal inflammatory reaction results from an increased recruitment of inflammatory cells and a prolonged survival of these cells in the nasal mucosa. This is due to interactions with adhesion molecules and probably altered apoptosis (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

2.3.3 Neurotransmitters

Neuropeptides, the non-adrenergic, non-cholinergic system peptide neurotransmitters, are presumed to be involved in the allergic reaction (Joos, Germonpre, Kips, Peleman, & Pauwels, 1994). However, the mechanism of the specific involvement of neuropeptides in AR needs to be further investigated.

Nitric oxide is an endogenous soluble gas acting as an intercellular transmitter. Nitric oxide has been observed to increase in the nose of AR patients (Kawamoto, Takeno, & Yajin, 1999; Martin, Bryden, Devoy, & Howarth, 1996), and sinusitis patients (Arnal et al., 1999). Nitric oxide may be an important mediator of the effector arm of the naso-nasal reflex that increases vascular permeability (Lane, Prazma, Baggett, Rose, & Pillsbury, 1997). Further studies are necessary to confirm the role of nitric oxide in AR.

2.3.4 The IgE immune response

Allergy is caused by a sustained overproduction of IgE in response to allergens. Increased serum IgE level is characteristic of atopic (inherited allergic condition)
diseases like AR. IgE production results from complex interactions between B-cells, T-cells, mast cells and basophils. It involves a series of surface molecules, as well as the presence of the IL-4 and IL-3 cytokines. In view of the location of the tissue distribution of these various types of cells, it is likely that IgE synthesis takes place not only in the germinal centres of the lymph node, but also in the nasal mucosa (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

IgE provokes immune response by binding to receptors found on the surface of mast cells and basophils, eosinophils, monocytes, macrophages and platelets in humans. There are two types of IgE receptors: FcεRI (the high-affinity IgE receptor) and FcεRII (CD23), (the low-affinity IgE receptor). IgE can upregulate the expression of both Fcε receptors. FcεRI is expressed only on mast cells and/or basophils. Aggregation of antigens and binding of IgE to the FcεRI on mast cells causes deregulations and the release of mediators from the cells, while basophils cross-linked with IgE release cytokines like interleukin-4 (IL-4) and interleukin-13 (IL-13) and other inflammatory mediators. The low affinity receptor (FcεRII) is always expressed on B cells, but its expression can be induced on the surfaces of macrophages, eosinophils, platelets and some T cells by IL-4. FcεRII allows the occurrence of facilitated antigen presentation, an IgE-dependent mechanism (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

2.3.5 From nasal challenge to chronic rhinitis

The allergic reaction after nasal challenge includes early and late-phase reactions.

- The early-phase reaction

Patients present symptoms such as rhinorrhoea, obstruction, sneezing and itchiness within minutes of a nasal challenge with pollen grains (Lebel et al., 1988). At this
stage, mast cells are activated, several mediators including histamine are released that induce symptoms of itchiness and sneezing, nasal mucosal blood flow decreases and plasma exudation causes nasal hypersecretion and congestion.

- The late-phase reaction

About 30-40% of patients will have a late-phase reaction in 4 to 12 hours after allergen challenge (Naclerio et al., 1985). Nasal obstruction is the main symptom at this stage, while rhinorrhoea and sneezing are less severe. The late-phase reaction is caused by the migration of other leukocytes such as neutrophils, lymphocytes, eosinophils and macrophages to the allergy site.

Another important phenomenon is called the “priming effect”. It has been found that during a single nasal challenge with pollen, the number of grains required to induce symptoms is much more than that inhaled during the pollen season (Lebel et al., 1988; Naclerio et al., 1983). On the other hand, in the second challenge the number of pollen grains required for inducing a positive result is much less than that in the first challenge. This is called a “priming effect” which can be mimicked by using challenge with very low repeated doses of allergen. The priming effect of nasal mucosa explains why once the nasal mucosa is primed by a high pollen count, a low pollen count later will also induce symptoms (Bousquet et al., 1991).

In summary, AR is an allergic reaction characterised by varying degrees of morbidity due to upper respiratory tract symptoms including sneezing, nasal congestion, rhinorrhoea and nasal itching. These symptoms are due to the interaction between the allergen and IgE causing immediate mast cell release of histamine and other mediators. Mediators, cytokines, chemokines, neuropeptides, adhesion molecules
and cells all co-operate in a complex network to induce the above symptoms of AR. This complicated process establishes the early and late-phase reactions of AR.

**2.4 Allergens and other risk factors**

AR is a multifactorial disease resulting from several factors including genetic factors, lifestyle and environmental factors such as allergens. This section introduces factors in the development of AR to explain the high and increasing prevalence of this disease.

**2.4.1 Allergens**

AR can be triggered by many kinds of allergens which are antigens inducing and reacting with specific IgE antibodies. Allergens include a range of animals, insects, plants, fungi and small molecular weight chemicals. Most of these allergens are proteins or glycoproteins (Savolainen, Viander, & Koivikko, 1990). They are classified as inhalant allergens, food allergens and occupational allergens as explained below (Bousquet, Khaltaev, et al., 2008).

**2.4.1.1 Inhalant allergens**

Inhalant allergens are usually classified as indoor and outdoor agents. The most commonly seen inhalant allergens are as follows:

a. Dust mites

House dust mites such as *Dermatophagoides* and *Euroglyphus* which feed on human skin dander are particularly abundant in mattresses, bed bases, pillows, carpets, furniture and fluffy toys (Bousquet, Van Cauwenberge, & Khaltaev, 2001). Patients who are allergic to these house dust mites have symptoms all year round with an aggravation during humid periods as these mites grow more in hot and humid
environments (Chan-Yeung et al., 1995). Furthermore, in very damp houses, storage mites may grow in stocked grains and flour and are usually present in the dust (Bernd, Ambrozio, & Baggio, 1996).
b. Pollens

The pollen grain is the mail sex cell of the vegetable kingdom. The anemophilous pollens which are transported by wind can travel hundreds of kilometres. Most patients are allergic to many different types of pollens. Pollen allergy is higher in rural areas than in urban area as per the pollen counts (Nicolaou, Siddique, & Custovic, 2005). The size of pollens varies from 10 to 100 µm in diameter. Therefore, pollen may deposit not only in the nostrils but also in the eyes. This explains the reason why pollen allergic patients usually have rhinitis and conjunctivitis (Suphioglu et al., 1992). The pollens causing most allergies are found among: grasses; certain weeds such as mugwort and ragweed; trees such as birch and other Betulaceae species, Oleaceae species (ash and olive trees), oak, plane tree, cypress tree, etc. In Melbourne, Australia, grass pollen especially that of ryegrass, has been proven to be the major source of airborne allergens causing AR (Schappi et al., 1999).

c. Animal dander

Cat and dog allergens are the major animal allergens for asthma, AR and rhinoconjunctivitis (Bousquet, Khaltaev, et al., 2008). Other animals such as rabbits, guinea pigs, rats or horses are also associated with AR symptoms (Bousquet, Khaltaev, et al., 2008). The most important allergen sources from animals are the sebaceous glands, saliva and the peri-anal glands. These allergens can be found in animal’s fur, saliva and urine and are transported in the air and remain airborne for a prolonged period. They are also adherent so that they can exist in the environment for weeks or months even after the animals have been taken away. Additionally, these allergens can be carried by clothing and transported to the areas where animals have no access such as schools and public buildings or even homes without animals (Bousquet, Khaltaev, et al., 2008).
d. Fungal allergens
Superior fungi, moulds and yeast release large quantities of allergenic spores into the indoor and outdoor environment (Bousquet, Khaltaev, et al., 2008). Fungi and moulds grow particularly well in hot and humid areas while yeast can be found in foods as well. The major outdoor moulds which cause allergy are Cladosporium, Alternaria and Stemphylium. In addition, domestic moulds which are mainly abundant in bathrooms and kitchens or in the areas which are watered frequently for plant growth also play an important role. Mould spores are able to enter deeply into the respiratory tract due to their small size. Therefore, AR as well as asthma can be triggered by mould allergens (Bousquet, Khaltaev, et al., 2008).

e. Insects
Once insect waste is inhaled into the respiratory tract, an IgE immune response can also been induced. Wastes of insects, such as cockroaches, usually are found in apartments or low-income houses (Cohn, Arbes, Jaramillo, Reid, & Zeldin, 2006; Leaderer et al., 2002; Lewis, Weiss, Platts-Mills, Syring, & Gold, 2001). Among the household allergens, in some hot and humid regions, allergies caused by cockroach waste, can have the same frequency as, or even a higher frequency than that caused by house dust mites (Barnes & Brenner, 1996; Lan, Lee, Wu, Chang, & Yeh, 1988; Sakaguchi et al., 1994).

2.4.1.2 Food allergens
Food allergens usually cause allergy with multiple organ involvement or even severe systemic anaphylaxis. Rhinitis is one of the common symptoms of food allergy. Milk, egg and soy are the major allergens for infants less than six months old while
peanuts, tree nuts, fish, egg, milk, sesame, celery and some fruits are the common allergens for adults (Bousquet, Bjorksten, et al., 1998).

Cross-reaction allergens between food and inhalant allergens are common. For example, patients who are allergic to birch or other Betulaceae pollens may also be allergic to tree nuts, fruits and vegetables (Eriksson, Formgren, & Svenonius, 1982; Geroldinger-Simic et al., 2011); ragweed or grass pollen sensitive patients may also present symptoms when eating banana or melon (Enberg, Leickly, McCullough, Bailey, & Ownby, 1987; Garcia Ortiz, Cosmes Martin, & Lopez-Asunolo, 1995).

2.4.1.3 Occupational agents

Occupational rhinitis is caused by agents in workplaces. For example, bakery allergens such as flour and grain may cause rhinitis to bakers; laboratory animals may induce AR symptoms in laboratory personnel (Bousquet, Khaltaev, et al., 2008). Latex allergy has become an increasing concern to cause occupational allergy due to the increasing use for industrial products and household items or medical devices (Bousquet, Flahault, et al., 2006).

2.4.2 Pollutants

Outdoor pollutants such as automobile pollution and organic chemical agents are associated with rhinitis symptoms (Hwang, Jaakkola, Lee, Lin, & Guo, 2006; Keles, Ilicali, & Deger, 1999). Indoor pollutants include biomass fuels, gas pollutants and compounds utilised during the manufacturing process of furniture may also cause AR (Karol, 1991). Similarly, tobacco smoke aggravates AR because smoking inconstantly increases the total and specific IgE (Wuthrich, Schindler, Medici, Zellweger, & Leuenberger, 1996).
2.4.3 Other risk factors of AR

In addition, other risk factors are related to AR. For example, a genetic component has been well established as a risk factor in AR (Bahna, 1992). People with a parent who has AR have an increased risk of developing AR themselves. The risk increases significantly if both parents have AR. Previous studies have demonstrated that there is a close association between childhood allergic disease and parental allergic history in populations (Barnes & Marsh, 1998). Furthermore, the ethnic origin may affect the AR prevalence. Surveys demonstrated that there are differences in AR prevalence between different ethnic populations in the same area in England (Gillam, Jarman, White, & Law, 1989) and New Zealand (Pattemore et al., 1989). However, this difference perhaps is caused by lifestyle and environmental factors. In contrast, another study showed that in the United States, there is a similar prevalence of AR in both Caucasian and black population (Sly, 2002). Furthermore, in recent years, climate changes became one of the factors caused the increasing of allergic disease (Beggs, 2010; Sheffield, Weinberger, & Kinney, 2011; Ziska et al., 2011).

In summary, an increasing worldwide prevalence in AR has been observed over the last few decades. The reasons for this phenomenon are still not understood completely. Many factors may be involved in the high and increasing prevalence of AR.

2.5 Classification of AR

There are two systems of classification of AR: 1. seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR); and 2. intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER).
2.5.1 SAR/PAR classification

This classification is based on the seasonality character of symptoms and allergens (Dykewicz et al., 1998). Symptoms of AR may occur only during specific seasons, be perennial without seasonal exacerbation, be perennial with seasonal exacerbation or may occur sporadically after specific exposures. Thus, AR is subdivided into SAR and PAR based on the tune of allergen exposure:

a. SAR is caused by an IgE-mediated reaction to seasonal aeroallergens.
   Typical seasonal aeroallergens are pollens. The length of seasonal exposure to these allergens depends on geographic location.

b. PAR is caused by an IgE-mediated reaction to perennial environmental aeroallergens. These allergens may include dust mites, moulds, animal allergens or certain occupational allergens, as well as pollen in areas where pollen is prevalent perennially.

However, this traditional SAR/PAR classification is not entirely satisfactory as (Bousquet, Van Cauwenberge, & Khaltaev, 2001):

- To differentiate between seasonal and perennial symptoms is often difficult;
- Some pollen allergens exposure may be long standing instead of being seasonal in some areas;
- The nasal inflammation can be prolonged for weeks after pollen exposure in patients with SAR;
- The exposure to some perennial allergens cannot be similar over the whole year, therefore, symptoms caused by such perennial allergens can be short term; and
- The majority of patients are sensitised to both pollens and perennial allergens.
2.5.2 IAR/PER classification

Another classification which was introduced by Allergic Rhinitis and its Impact on Asthma (ARIA) in 2001 is based on the duration of symptoms and quality of life in the assessment of severity instead of the allergens. Therefore AR is divided into IAR or PER.

According to this classification, “Intermittent” AR (IAR) means the symptoms present less than four days a week or last for less than four consecutive weeks, while “Persistent” (PER) refers to symptoms present for more than four days a week and last for more than four consecutive weeks (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

With this classification, the severity of AR is categorised as “mild” or “moderate – severe” based on the quality of life (Bousquet, Van Cauwenberge, & Khaltaev, 2001). “Mild” means that none of the following items are present:

- Sleep disturbance,
- Impairment of daily activities, leisure and/or sport,
- Impairment of school or work,
- Troublesome symptoms.

“Moderate–severe” means that one or more of the above-mentioned items present.

A two-step cross-sectional, population-based, epidemiologic study in six Western European countries showed that the proportion for IAR/PER and SAR/PAR is quite consistent (Bauchau & Durham, 2005). Another study found that the classic types of SAR/PAR classification cannot be used interchangeably with the new classification of
IAR/PER because they do not represent the same stratum of disease (Alyasin & Amin, 2007).

Since the introduction of the IAR/PER classification, questions have arisen such as:

a. This classification must be performed in patients who are not under treatment. Therefore, how should we classify the AR patients who are under treatment (Valero et al., 2007)?

b. For the patients who are classified as “persistent” with symptoms presenting more than 4 days a week and lasting for more than 4 consecutive weeks, is there any difference between suffering symptoms for 6, 24, or 36 weeks (Valero et al., 2007)?

c. Is it really necessary to differentiate patients classified as moderate-severe? Does it help with the clinical management of AR (Valero et al., 2007)?

The mild/moderate–severe classification system of the symptom severity may not be adequate as most AR patients would be classified as the moderate-severe type based on this method. Some studies have analysed the prevalence of mild and moderate-severe rhinitis in different population samples and found that 69% of patients with rhinitis who attend an ear-nose-throat (ENT) or allergy clinic and 90% of the patients who attend a primary care centre are classified as Moderate-Severe (Bachert, van Cauwenberge, Olbrecht, & van Schoor, 2006; Bousquet et al., 2005; Bousquet, Neukirch, et al., 2006; Valero et al., 2007). Therefore, the “British Society for Allergy and Clinical Immunology (BSACI) guidelines for the management of allergic and non-allergic rhinitis” recommends
using the clinical classification of SAR/PAR alongside the ARIA’s IAR/PER classification (Scadding, 2008).

In Australia, the SAR/PAR classification is well-known and accepted by clinical practitioners and patients. With a cool temperate climate, the Melbourne area has a clearly high pollen count period during spring and summer. Hence, in the pollen season every year, scientists in the School of Botany, Melbourne University take daily measurements of the pollen levels in Melbourne, which are combined with the weather forecast to produce a pollen forecast. Pollen counts and predictions are rated as low, moderate, high or extreme levels (Schäppi, Taylor, Kenrick, Staff, & Suphioglu, 1998). On the days with high or extreme pollen counts, it is likely that people who are grass-pollen-sensitive will experience AR symptoms and they are suggested to stay indoors (Schäppi, Taylor, Kenrick, Staff, & Suphioglu, 1998).

Due to the above mentioned reasons, in this study, the SAR/PAR classification method was adopted for the recruitment of participants. That is, the study lasted for a whole year, during the pollen season, SAR patients were recruited and outside the pollen season, PAR patients were recruited.

2.6 Co-morbid conditions of AR

AR often coexists with other disorders, such as asthma, allergic conjunctivitis, sinusitis, nasal polyps and otitis media (Bousquet, Khaltaev, et al., 2008). The co-morbidity of AR also has an impact on patients’ quality of life and economic burden. This section introduces the relationship between AR and other co-morbid conditions.
2.6.1 Asthma

Epidemiological studies have concluded that most asthmatics have rhinitis and also many rhinitis patients have asthma (American Thoracic Society Workshop, 1999; Vignola, Chanez, Godard, & Bousquet, 1998). The prevalence of asthma has increased in rhinitis, especially in persistent rhinitis. It is suggested that “one airway one disease” be used to describe the close relationship between asthma and AR. The principle is that the two conditions are manifestations of one syndrome in two parts of the respiratory tract and that the more severe the rhinitis, the more severe the asthma (Bachert et al., 2004; Bousquet, Jacot, Vignola, Bachert, & Van Cauwenberge, 2004; Togias, 2003).

Asthma and AR share common risk factors. Allergens such as house mite or animal dander and occupational agents can cause both of these two conditions. Asthma and rhinitis have commonalities in mechanisms such as eosinophilic inflammation in the nasal and bronchial mucosa. Besides the inflammatory process, the nose plays the role of a protector for the lungs through warming and humidification, filtering, mucociliary clearance and air conditioning of the lower airways. These protective functions of the nose may explain some of the links between rhinitis and asthma (Bousquet, Khaltaev, et al., 2008).

The close relationship between asthma and rhinitis is due to the similarities of the nasal and bronchial mucosa (Togias, 2003). Both nasal and bronchial mucosa are characterised by a pseudostratified epithelium with columnar, ciliated cells resting on a basement membrane. In the submucosa underneath the epithelium, there are vessels, mucosa glands, some inflammatory cells and nerves. In asthma and rhinitis, inflammation of the nasal and bronchial mucosa is sustained by a similar
inflammatory infiltrate including eosinophils, mast cells, T lymphocytes, cells of the monocytic lineage, similar pro-inflammatory mediators, Th2 cytokines and chemokines. The presence of AR commonly aggravates asthma, and increases the risk of asthma attacks, emergency visits and hospitalisations for asthma (Bousquet, Khaltaev, et al., 2008). The inflammatory reaction of the nose can cause a worsening of asthma. This may be due to two reasons:

a. the nasal challenge induces the release of mediators, and

b. the post-nasal mucosa drip may induce inflammation of the lower airways.

Clinically, nasal symptoms occur early in the pollen season and reach a maximum level with peak pollen count or just after it while bronchial symptoms usually begin after the onset of the pollen season, peak later than the peak pollen counts period and persist for some time after (Welsh et al., 1987).

Moreover, AR is not only correlated to but is also a risk factor for asthma (Bousquet, Van Cauwenberge, & Khaltaev, 2001). Asthma develops more commonly in patients with AR than others who have no AR. On the other hand, the prevention or early treatment of AR may help to prevent the occurrence of asthma (Bousquet, Khaltaev, et al., 2008). It has been recommended by the 1999 World Health Organisation (WHO) workshop “ARIA” (Bousquet, Van Cauwenberge, & Khaltaev, 2001) that:

a. Patients with PER should be evaluated for asthma;

b. Patients with asthma should have examination of the upper respiratory tract for AR; and

c. A combination treatment for both the upper and lower airway disease is suggested.
In terms of treatment, intranasal glucocorticosteroids are the most effective topically administered drugs for the treatment of both rhinitis and asthma. Oral-H\_1-antihistamines are the first-line treatment for AR, however, are less effective for asthma (Bousquet, Khaltaev, et al., 2008).

### 2.6.2 Allergic conjunctivitis

Allergic conjunctivitis is a common co-morbidity of AR characterised as “red eye”. Allergic conjunctivitis is more common with outdoor allergens than indoor allergens; thus, it is usually seen in SAR.

The occurrence of conjunctivitis can be explained through the naso-conjunctival reflexes mechanism (Bousquet, Van Cauwenberge, & Khaltaev, 2001). It is also because the nose and eyes share a common pathophysiological background. Therefore, it is suggested that eye examination should be part of the clinical assessment of AR.

### 2.6.3 Sinusitis and nasal polyposis

Rhinosinusitis is a common complication of AR. This is possibly due to allergens entering the sinuses resulting in a similar allergic inflammation to that in the nasal mucosa (Karlsson & Holmberg, 1994). Although the role of allergy in sinus diseases remains unclear, adding antiallergic therapy to the treatment of chronic sinus disease is still helpful (Bousquet, Khaltaev, et al., 2008). Nasal polyps are considered as a chronic inflammatory disease of the sinonasal mucosa. The mucosa swelling and the sinonasal mucosa’s protrusion into the nasal cavity caused by allergic reaction may result in nasal polyps.
2.6.4 Otitis media with effusion

Otitis media with effusion is an inflammatory disease of the middle ear mucosa. Anatomically, the nose and middle ears are situated in a system of contiguous organs. Both cavities are covered by respiratory mucosa and there is continuity between these two cavities through the Eustachian tube. Respiratory allergy symptoms are risk factors for the development of otitis media with effusion (Chantzi et al., 2006).

2.6.5 Chronic cough

Chronic cough (over eight weeks) can be caused by a number of factors including AR. Of the AR symptoms, post nasal drip may be the most common cause of chronic cough (Pratter, 2006). Treatment with steroid nasal spray (Gawchik, Goldstein, Prenner, & John, 2003) or oral H1-antihistamine is effective for chronic cough on AR patients (Ciprandi et al., 1997).

Apart from the conditions described above, other disorders such as adenoid hypertrophy, tubal dysfunction, laryngitis, and gastro oesophageal reflux are also considered to be associated with AR (Bousquet, Khaltaev, et al., 2008).

2.7 Impacts of AR

This section provides details of the impacts of AR on patients’ quality of life and the broader social and economic impacts.
2.7.1 Impacts on quality of life

It has been reported that allergic reaction causes significant fatigue and mood changes (Marshall, O'Hara, & Steinberg, 2002), some impairment of cognitive function (Kremer, den Hartog, & Jolles, 2002; Marshall, O'Hara, & Steinberg, 2000), depression and anxiety (Cuffel, Wamboldt, Borish, Kennedy, & Crystal-Peters, 1999; Bavbek, Kumbasar, Tugcu, & Misirligil 2002). AR not only results in the classical symptoms of sneezing, rhinorrhea and nasal obstruction, but also is associated with impairments in how patients function in daily life (Kirmaz et al., 2005). AR affects patients’ quality of life in several important domains, reduces sufferers’ work productivities and limits social activities (Bousquet et al., 1994). A study on “health-related quality of life” of AR patients reported that the most common complaints for adults with rhinitis were: being not able to sleep well at night, often feeling tired and worn out during the day, practical problems and being limited in daily activities. For adolescents, the major problem caused by AR was lack of concentration with school and work, whilst for children, being bothered by symptoms and impaired learning, memory and behaviour were the main difficulties caused by AR (Juniper, 2001). The main ways in which AR has an impact on quality of life are as follows:

- Sleep disturbance
  Poorly controlled AR may lead to sleep loss or disturbance. On the other hand, using sedative treatment may increase patients’ daytime sleepiness.

- Learning disability
  Children with uncontrolled AR may have learning problems during school hours either by direct interference or by sleep loss resulting in daytime fatigue (Craig, Teets, Lehman, Chinchilli, & Zwillich, 1998; Simons, 1996).

- Work impairment
AR may induce work absenteeism and reduce work productivity. Patients may suffer from fatigue, poor performance and loss of concentration at work; headaches and conjunctivitis may impair vision or vision-related activities. In addition, some medications such as sedating antihistamines may reduce workers’ functioning.

2.7.2 Economic burden of AR

AR causes significant economic impacts on the affected persons and their families, on the health care systems and on the whole society. In evaluating the economic burden, the cost of illness approach included both direct costs such as the expenses associated with medical care for the illness, and indirect costs such as the costs resulting from non-medical losses as a consequence of the illness. The economic impact of AR is often underestimated for the reason that the substantial indirect costs of the disease are not well evaluated (Bousquet, Khaltaev, et al., 2008).

In Australia, the financial burden of allergies is significant. According to the data from Australasian Society of Clinical Immunology and Allergy, in 2007 the total annual cost of allergies was calculated as $7.8 billion. It was broken down into: the cost due to lower productivity ("presenteeism" $4.2 billion), direct medical costs ($1.2 billion), lower employment rates ($1.1 billion), absenteeism and lost household productivity ($0.2 billion) and premature death ($83 million). Forty-nine per cent (49%) of the financial costs of allergic disease were borne by individuals with allergies and their families. Overall, patients with allergies spend over $120 million/year on over-the-counter allergy medications. If the cost of wellbeing is included, allergic patients would bear 86% of the costs (Australasian Society of Clinical Immunology and Allergy (ASCIA), 2007).
However, much of the costs associated with rhinitis may be underestimated due to the frequent use of over-the-counter medications (Malone, Lawson, Smith, Arrighi, & Battista, 1997). A recent survey in the United States concluded that the burden of AR in children has been significantly underestimated as the health care practitioners overestimate patients’ and parents’ satisfaction with disease management (Meltzer et al., 2009).

2.7.3 Cost-effectiveness study

As AR significantly impairs patients’ quality of life, quality of life measurements need to be taken into consideration in clinical trials and when treating patients. Recently, there is an increasing interest in cost-effectiveness studies due to the high prevalence of AR and concern about health care costs. For example, it has been found that the first generation oral H1-antihistamine is not cost-effective because of the cost of associated sedation (Sullivan, Follin, & Nichol, 2004). Recently, a study investigated the cost-effectiveness of acupuncture for AR transformed the value of the Short Form 36 Health Survey (SF-36) into health-status utilities for cost-effectiveness analysis (Witt, Reinhold, Jena, Brinkhaus, & Willich, 2009).

2.8 Diagnosis of AR

The diagnosis of AR is based on the concordance between a typical history of allergic symptoms and diagnostic tests.

2.8.1 Symptoms

Major symptoms of AR include sneezing, anterior rhinorrhea and bilateral nasal obstruction. For patients with pollen-induced AR, eye symptoms are also very
common. Patients who have two or more of the following symptoms need to be considered for a diagnosis of AR: watery rhinorrhea, sneezing, nasal obstruction, nasal pruritus and with or without conjunctivitis (ARIA, 2001).

Rhinitis patients are usually divided into “sneezers and runners” and “blockers” groups. In AR, “sneezers and runners” are more commonly seen in SAR while “blockers” are more common in PAR (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

Some associated symptoms should also be taken into account in AR diagnosis. These are: decreased sense of smell, snoring, sleeping problems, headache, postnasal drip or chronic cough and sedation, all of which may be caused by the rhinitis itself.

2.8.2 Case history

A typical clinical history of AR symptoms is important for the diagnosis of AR and for the assessment of its severity as well. Usually patients would have a conjecture regarding the substances causing their AR symptoms. The case history should focus on the evidence of the origin of this condition, whether it is allergic or non-allergic, identification of the possible allergens and time period of worsening or any trigger factors of occurrence to support the diagnosis. This history should also include questions about the symptom frequency, severity, duration, persistence or intermittence and seasonality (Bousquet, Khaltaev, et al., 2008).
2.8.3 Family history

It is documented that family history is an important risk factor for AR. For a child whose parents both have a history of atopy (inherited allergic condition), the chance of developing AR is greater than those with only one parent who is atopic (Dykewicz et al., 1998).

2.8.4 General ENT examination

For AR patients, a nasal examination is optimal. When needed, anterior rhinoscopy examination or nasal endoscopy should be applied to describe the anatomical situation in the nose, the colour of the mucosa and the amount and aspect of the mucus. In AR cases, bilateral but not always symmetrical swelling can be observed; the mucosa of the middle meatus may be seen; the mucosa is usually of a common pale colour. Sometimes a major oedema of the nasal mucosa can make the study of the nose impossible and an increase in vascularity is also commonly seen. There is usually no increase in abnormal anatomical structure in the noses of AR patients. On the other hand, without allergen exposure, AR patients’ nasal mucosa may seem normal (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

2.8.5 Skin tests

Skin allergy tests are a procedure that involves applying a microscopic amount of an allergen to patients’ skin by various means: scratch tests, prick and puncture tests, intradermal skin tests, prick-prick tests and atopy patch tests. If an immune-response is seen in the form of a rash, hives or even anaphylaxis, it can be concluded that the patient has an allergy to the particular allergen. Among these skin tests, the modified skin prick test introduced by Pepys (Nelson, 2009) is currently recommended for the
clinical diagnosis of IgE-mediated allergic diseases. In the skin prick test, a small drop of the purified allergen is placed on to the skin surface (usually the forearm) with a gentle prick on the skin. This test is usually performed in order to identify allergies to pet dander, dust, pollen, foods or dust mites. It is suggested that the skin prick test is the simplest and most convenient test to perform and currently has the highest sensitivity to ascertain the AR diagnosis (Bernstein & Storms, 1995; Bousquet, Van Cauwenberge, & Khaltaev, 2001). However, its high sensitivity also brings the problem of low specificity. It may induce some false positive reactions (Dreborg, 1989). Other skin tests such as scratch tests are not recommended to be used any longer due to poor reproducibility; skin puncture tests may decrease the variability of skin prick test but need greater skill; intradermal skin tests are more sensitive than prick tests, however, they may induce some false reactions and they are less well correlated with symptoms (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

The skin tests should be performed by trained personnel following a rigorous methodology. When skin tests are applied, negative and positive controls are necessary to reduce false reactions. In addition, the proper interpretation of results requires a thorough knowledge of the history and physical findings. Therefore, skin prick test on its own cannot be used to confirm a definite clinical reactivity to an allergen.

2.8.6 IgE tests

IgE tests can be applied by testing serum-total IgE, serum-specific IgE and nasal-specific IgE. The measurement of serum-total IgE should no longer be used for screening or diagnosis as allergic, parasitic diseases and many other conditions increase the levels of total IgE in serum. The measurement of serum-specific IgE is
important as its results correlate closely to those of skin tests and nasal challenges. A radioallergosorbent test (RAST test) is a blood test to detect specific IgE antibodies to certain allergens. It has been used as an alternative to the skin tests to clarify an allergy. Some AR patients may have a local IgE immune response without any systemic release of IgE. Skin tests or serum-specific IgE tests may have negative results in these cases, therefore a further nasal-specific IgE test will be needed (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

2.8.7 Nasal challenge tests

For standardised allergens, challenges are not usually necessary to confirm the diagnosis of common inhalant allergy. However, challenge tests are more important in the diagnosis of occupational rhinitis.

In summary, the diagnostic approach introduced by WHO is as below: for most patients, a precise and complete history of allergic symptoms, a nasal examination and a limited number of skin tests are all required for diagnosing allergic aetiology and the relevant allergen exposure. If there is discordance between the history and the skin prick test, further tests are suggested (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

2.9 Current management of AR

Many AR patients do not consult with medical doctors and only use over-the-counter drugs. Some commonly seek self-treatment for symptomatic relief or use unproven alternative therapies. Hence their symptoms do not always get well managed. It is important to understand an appropriate initial treatment strategy of AR so that a treatment plan can be tailored to individual needs of the patients in clinical practice.
The current management of AR consists of allergen avoidance, pharmacotherapy and allergen-specific immunotherapy (Bousquet, Khaltaev, et al., 2008).

2.9.1 Allergen avoidance

As AR symptoms are caused by inflammation of the nasal mucus membrane after exposure to specific allergens, the avoidance of the allergens may reduce provoking AR symptoms. For example, for the patients who are allergic to animal fur, avoidance of animals is effective for symptom relief.

Improving indoor air quality is also important. Recommendations include improving ventilation, refining cleaning methods and housing hygiene, avoiding wall-to-wall carpeting, using moisture control to prevent the accumulation of mould and controlling the sources of pollution such as tobacco smoke and emissions from buildings and consumer products (Franchi et al., 2006).

However, to completely avoid the inhalant allergens such as pollen, dust, and pollutants which exist in the air is impossible in people’s daily life. For instance, patients who are allergic to animals may benefit from allergen avoidance at home; but they may encounter allergens in public transportation, schools and public places (Bousquet, Khaltaev, et al., 2008).

2.9.2 Pharmacotherapy

Pharmacologic treatment should take the following factors into account: efficacy, safety, cost-effectiveness of medications, patient’s preference, objective of the treatment, likely adherence to recommendations and the presence of co-morbidities.
Rhinitis medications are administered intranasally or orally in most cases. Intranasal medications have high concentrations and can be used directly into the nose thus avoiding or minimising systemic effects. In patients who also have conjunctivitis and/or asthma, medications need to be used to address these aspects, not only to relieve the nasal symptoms (Bousquet, Khaltaev, et al., 2008). Details on the current pharmaceutical management for AR are provided in 2.9.2.1 to 2.9.2.4 below.

2.9.2.1 Antihistamines

Although a number of mediators are involved in the pathophysiology of allergic symptoms, histamine still remains the major one. Therefore, the most commonly prescribed medications for AR are antihistamines. Antihistamine can be applied through oral and topical pathways.

Antihistamines were discovered in 1937 by Bovet and Staub at the Institute Pasteur (Emanuel, 1999) and were first used for human treatment of allergic diseases in 1942. Clinically, antihistamines can be administered orally or topically. When administered orally, an H1-antihistamine exerts its effects on both nasal and non-nasal symptoms such as conjunctivitis. The first generation of antihistamines (before 1980) had more severe side effects compared with the second generation of antihistamines and thus the first generation is no longer recommended for the treatment of AR. The most common side effect is sedation. The second generation H1-antihistamines are highly selective to the H1-receptors and are therefore effective in reducing itching, sneezing and watery rhinorrhea. Most of the second generation H1-antihistamines have an acute onset of action and their effects last for up to 24 hours. Therefore, the second generation oral or intranasal H1-antihistamines are
recommended for the treatment of AR and conjunctivitis in adults and children. However, the second generation of antihistamines are less effective on nasal obstruction as they do not reduce vasodilatation (van Cauwenberge et al., 2000). On the other hand, not all second generation anti-histamines are free from side effects, even though they are mostly devoid of central nervous system side effects. Some side effects have been observed such as: cardiac side effects, carcinogenic effects, appetite stimulation and weight gain, and gastrointestinal disturbances (van Cauwenberge et al., 2000).

2.9.2.2 Glucocorticosteroids

Glucocorticosteroids are the most effective drugs available for the clinical management of AR. They can be administered through both systemic and topical routes. Since the risk of adverse effects from systemic glucocorticosteroids is related to the duration of treatment, it is suggested that only infrequent short-term courses should be prescribed for rhinitis. Clinically, topical glucocorticosteroids are more frequently used for rhinitis. Topical glucocorticosteroids were first applied as a nasal spray for SAR in 1973 when beclomethasone was introduced (Mygind, 1973). Currently, intranasal glucocorticosteroids are the most potent medication available for allergic and non-allergic rhinitis. In three international reports, intranasal glucocorticosteroids are considered as a first-line therapy for adults in moderate and severe cases of AR (Dykewicz, 1998; International Rhinitis Management Working Group, 1994; van Cauwenberge, 2000).

The effects of glucocorticosteroids on AR are caused by the anti-inflammatory and other effects. Side effects of intranasal glucocorticosteroids are mainly local effects such as crusting, dryness, minor epistaxis or medication-dependence (Bousquet,
Van Cauwenberge, & Khaltaev, 2001; Holm et al., 1998; LaForce, 1999). Also, the intranasal medication cannot be given when the nostril is completely blocked (Bousquet, Van Cauwenberge, & Khaltaev, 2001).

2.9.2.3 Chromones

Mast cells have an important role in both the early and late phase of allergic responses of AR. Mast cell stabiliser such as Chromones has been shown to be effective in improving sneezing, watery rhinorrhoea and nasal itching. However, they are not superior to topical glucocorticosteroids or H1-antihistamine (van Cauwenberge 2000). Chromones were discovered from the medical plant Ammi visnaga. Chromones can be administered via nasal and ocular route. In adults, chromones are not a major therapeutic option due to being less effective than H1-antihistimine or intranasal glucocorticosteroids (Meltzer, 2002; Schuller et al., 1990).

2.9.2.4 Decongestants

Decongestants, also known as vasoconstrictor drugs, can rapidly relieve nasal obstruction due to the function of vasoconstriction by their action on α-adrenergic receptors. They can be administered either orally or topically. Clinically, decongestants are always applied in combination with anti-histamine (Anolik, 2009; Grubbe, Lumry, & Anolik, 2009).

Decongestants are associated with systemic side effects such as heart diseases, hypertension, insomnia, irritability, renal failure, psychosis, stroke etc. Therefore, it is recommended that the use of decongestants should be limited to within one week. Other nasal side effects including nasal burning, stinging, dryness or mucosal
ulcerations and even septal perforations may occur after the use of intranasal decongestants (Bousquet, Van Cauwenberge, & Khaltiev, 2001).

It is recommended by the ARIA guidelines that the treatment for AR should be tailored according to the individual patient’s symptom severity, co-morbidities, the availability and affordability of treatment and patient’s preference (Bousquet, Khaltiev, et al., 2008) (See Figure 5).

(Adapted from “ARIA in the pharmacy: management of allergic rhinitis symptoms in the pharmacy” (ARIA, 2004))

**Figure 5: Management of AR in the pharmacy**

The commonly used medications with their mechanisms and side effects are summarised in the Table 2 below.
Table 2: Glossary of medications used in AR

<table>
<thead>
<tr>
<th>Name and also known as</th>
<th>Generic name</th>
<th>Mechanism of action</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral H1-antihistamines</td>
<td><strong>Second generation</strong>&lt;br&gt;Acrivastine, Azelastine, Cetirizine, Desloratadine, Ebastine, Fexofenadine, Levocetirizine, Loratadine, Mequitazine, Mizolastine, Rupatadine</td>
<td>Blockage of H1 receptor&lt;br&gt;Some anti-allergic activity&lt;br&gt;New generation drugs can be used OD&lt;br&gt;No development of tachyphylaxis</td>
<td><strong>Second generation</strong>&lt;br&gt;No sedation for most drugs&lt;br&gt;No anticholinergic effect&lt;br&gt;No cardiotoxicity for products still available&lt;br&gt;Acrivastine has sedation effects&lt;br&gt;Mequitazine has an anticholinergic effect&lt;br&gt;<strong>First generation</strong>&lt;br&gt;Sedation is common and/or anticholinergic effect</td>
<td>Second generation H1-antihistamine should be preferred for their favourable efficacy/safety ratio and pharmacokinetics&lt;br&gt;Rapid effective (&lt;1h) on nasal and ocular symptoms&lt;br&gt;Moderately effective on nasal congestion&lt;br&gt;Cardiotoxic drugs are no longer marketed in most countries</td>
</tr>
<tr>
<td></td>
<td><strong>First generation</strong>&lt;br&gt;Chlorphenyramine, Clemastine, Dimethindene maleate, Hydroxyzine, Ketotifen, Oxatomine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local H1-antihistamine (intranasal, intraocular)</td>
<td>Azelastine, Levocabastine, Olopatadine</td>
<td>Blockage of H1 receptor&lt;br&gt;Some anti-allergic activity for azelastine</td>
<td>Minor local side effects&lt;br&gt;Azelastine: bitter taste</td>
<td>Rapidly effect (&lt;30min) on nasal or ocular symptoms</td>
</tr>
<tr>
<td>Intranasal glucocorticosteroids</td>
<td>Beclomethasone dipropionate, Budesonide, Ciclesonide, Flunisolide, Fluticasone propionate, Fluticasone furoate, Mometasone furoate, Triamcinolone acetonide</td>
<td>Potently reduce nasal inflammation&lt;br&gt;Reduce nasal hyperreactivity</td>
<td>Minor local side effects&lt;br&gt;Wide margin for systemic side effects&lt;br&gt;Growth concerns with beclomethasone dipropionate only in young children</td>
<td>The most effective pharmacologic treatment of AR&lt;br&gt;Effective on nasal congestion&lt;br&gt;Effective on smell&lt;br&gt;Effect observed after 12 h but maximal effect after a few days</td>
</tr>
<tr>
<td>Name and also known as</td>
<td>Generic name</td>
<td>Mechanism of action</td>
<td>Side effects</td>
<td>Comments</td>
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<td>------------------------</td>
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<tr>
<td>Leuktriene antagonists</td>
<td>Montelukast, Pranlukast, Zafirlukast</td>
<td>Block CystLT receptor</td>
<td>Excellent tolerance</td>
<td>Effective on rhinitis and asthma&lt;br&gt;Effective on all symptoms of rhinitis and on ocular symptoms</td>
</tr>
<tr>
<td>Local cromones (intranasal, intraocular)</td>
<td>Cromoglycate, Nedocromil, NAAGA</td>
<td>Mechanism of action poorly known</td>
<td>Minor local side effects</td>
<td>Intraocular cromones are very effective&lt;br&gt;Intranasal cromones are less effective and their effect is short lasting&lt;br&gt;Overall excellent safety</td>
</tr>
<tr>
<td>Oral decongestants</td>
<td>Ephedrine, Phenylephrine, Phenyl propanolamine, Pseudoephedrine, Oral H1-antihistamine-decongestant combinations</td>
<td>Sympathomimetic drugs Relieve symptoms of nasal congestion</td>
<td>Hypertension&lt;br&gt;Palpitations&lt;br&gt;Restlessness&lt;br&gt;Agitation&lt;br&gt;Tremor&lt;br&gt;Insomnia&lt;br&gt;Headache&lt;br&gt;Dry mucous membrane&lt;br&gt;Urinary retention&lt;br&gt;Exacerbation of glaucoma or thyrotoxicosis</td>
<td>Use oral decongestants with caution in patients with heart disease&lt;br&gt;Oral H1-antihistamine-decongestant combination products may be more effective than either product alone but side effects are combined</td>
</tr>
<tr>
<td>Intranasal decongestants</td>
<td>Oxymethazoline, Xylomethazoline, others</td>
<td>Sympathomimetic drugs Relieve symptoms of nasal congestion</td>
<td>Same side effects as oral decongestants but less intense&lt;br&gt;Rhinitis medicamentosa is a rebound phenomenon occurring with prolonged use (over 10 days)</td>
<td>Act more rapidly and more effectively than oral decongestants&lt;br&gt;Limit duration of treatment to &lt;10 days to avoid rhinitis medicamentosa</td>
</tr>
<tr>
<td>Name and also known as</td>
<td>Generic name</td>
<td>Mechanism of action</td>
<td>Side effects</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
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<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>Oral/IM glucocorticosteroids</td>
<td>Dexamethasone, Hydrocortisone, Prednisolone, Prednisone, Triamcinolone</td>
<td>Potently reduce nasal inflammation Reduce nasal hyperreactivity</td>
<td>Systemic side effects common in particular for IM drugs Depot injections may cause local tissue atrophy</td>
<td>When possible, intranasal glucocorticosteroids should replace oral or IM drugs However, a short course of oral glucocorticosteroids may be needed if moderate/severe symptoms</td>
</tr>
<tr>
<td>Intranasal anticholinergics</td>
<td>Ipratropium</td>
<td>Anticholinergics block almost exclusively rhinorrhea</td>
<td>Minor local side effects Almost no systemic anticholinergic activity</td>
<td>Effective on allergic and nonallergic patients with rhinorrhea</td>
</tr>
</tbody>
</table>

(Adapted from “ARIA Executive summary of the workshop report” (Bachert, van Cauwenberge, & Khaltaev, 2002))
2.9.3 Allergen-specific immunotherapy

Allergen specific immunotherapy is the practice of administering gradually increasing quantities of an allergen vaccine to an allergic subject in order to reduce symptoms associated with subsequent exposure to allergens. Allergen immunotherapy was introduced in 1911 by Noon and Freeman to treat “pollinosis” or AR (Noon, 1911). There has been some evidence that immunotherapy using inhalant allergens to treat SAR or PAR is clinically effective (Bousquet, Lockey, et al., 1998). This method can induce clinical and immunologic tolerance therefore has a long-term effect and may prevent the allergic diseases’ progressing.

Guidelines and indications for specific immunotherapy with inhalant allergens have been published over the past years by WHO, the European Academy of Allergy and Clinical Immunology, the International Consensus Report on Asthma, the Global Strategy for Asthma Management and Prevention, the International Consensus Report on Rhinitis, the British Society for Allergy and Clinical Immunology, the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology (Bousquet, Khaltaev, et al., 2008). These reports provide guidelines for a better understanding of the use of allergen specific immunotherapy. It is suggested that immunotherapy should be initiated early in the disease process to reduce the risk of side effects and to prevent the further development of severe diseases.

Traditionally, the allergen specific immunotherapy is administered subcutaneously. It has been well established for both rhinitis and asthma. The efficacy of subcutaneous immunotherapy has been proven (Calderon et al., 2007). However, applying subcutaneous immunotherapy should be under a strict strategy as it is burdened with
the risk of causing systemic side effects. These side effects may be life-threatening (Bousquet, Khaltaev, et al., 2008).

Another approach of specific immunotherapy currently available in some countries is sublingual immunotherapy. However, the efficacy and safety of sublingual immunotherapy is still controversial. More studies comparing these two routes of immunotherapy are needed.

2.9.4 Anti-IgE

Anti-IgE forms complexes with free IgE, blocking its interaction with mast cells and basophils and lowering free IgE levels. Anti-IgE may induce rare but potentially severe anaphylactic reactions (Price & Hamilton, 2007). It is suggested that this therapy should be administered only in a healthcare setting with direct medical supervision (Bousquet, Khaltaev, et al., 2008).

2.9.5 Surgical treatment of rhinitis

Surgical treatment is not a part of standard AR management as it does not reduce allergy. For the patients with PAR, an inferior turbinates and some increase in glandular structure may occur. Therefore, the surgical reduction of the inferior turbinate body and mucosal surface will be helpful for reducing nasal obstruction and secretion. However, nasal surgery should only be considered when drug treatment is not effective and anatomical structure variations are present (Bousquet, Khaltaev, et al., 2008).
2.9.6 Alternative therapies for AR

Complementary and alternative medicine (CAM) has been widely used in Australia and many patients appear to be satisfied with the effectiveness of these therapies (Xue et al., 2008). AR is one of the conditions for which people seek CAM therapies, including acupuncture and CHM (Xue, English, Zhang, Da Costa, & Li, 2002). It has been reported by the WHO that acupuncture is regarded as effective for AR (World Health Organization (WHO), 1995).

A survey conducted in Germany (Schafer, Riehle, Wichmann, & Ring, 2002) found that among the participants who used alternative medicine for allergic conditions, the motivations or seeking alternative medicine included the assumption of few side-effects (78.3%), wish to try everything (71.7%) and unsatisfying results from conventional therapies (66.3%). This survey also reported that among all the allergic conditions, AR was the one most commonly treated by CAM therapies, and acupuncture was frequently used as a CAM therapy.

More details of the acupuncture and CHM management for AR are included in the reviews in Chapter 3.

2.10 Assessment of treatment effects

In clinical management and clinical research of AR, there are a number of instruments that are used to compare the severity of symptoms or patients’ quality of life before and after treatment in order to evaluate the treatment effects. The main instruments are detailed below.
2.10.1 Instruments for assessing symptom severity

Scoring systems are commonly used to record the severity of AR symptoms. By comparing the scores before and after treatment, the treatment effects are determined. Some scoring systems were recommended by ARIA (Bousquet, Khaltaev, et al., 2008).

2.10.1.1 Simple rating scale

A simple rating scale from 0 to 4 (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) of symptom severity assessment has been often used as an outcome measure in AR clinical trials since 1996 (Prenner et al., 1996; Xue, English, Zhang, Da Costa, & Li, 2002; Xue et al., 2007). Another 4 point scale (0 to 3) has also been frequently employed in clinical studies (Chui, Shek, Fong, Szeto, & Chan, 2010; Ng et al., 2004; Yang, Yu, Chen, Chiao, & Chen, 2010). It is suggested by Juniper et al. (Juniper et al., 2005) that the following simple rating scales can be used for clinical trials. It has defined criteria to enable assignment of the appropriate rating, as follows:

- 0 = no symptoms;
- 1 = mild symptoms (symptoms that are present but not particularly bothersome);
- 2 = moderate symptoms (symptoms that are bothersome but do not interfere with daily activities) and
- 3 = severe symptoms (symptoms that are bothersome and interfere with daily activities or disturb sleep).

This simple rating scale can be used to assess the severity of symptoms such as sneezing, nasal itch, nasal discharge and nasal obstruction (Juniper et al., 2005).
2.10.1.2 Visual Analogue Scale (VAS)

Two developed VAS questionnaires are also recommended by ARIA as outcome measures for AR (Bousquet, Khaltaev, et al., 2008).

a. Spector 7 point VAS (Spector et al., 2003)

This 7 point VAS was proposed by the Joint Task Force on Practice Parameters for the symptom severity assessment of AR. The questionnaire consists of several VAS for assessment of nasal symptom severity (individually for sneezing, running nose, congestion, itchy nose, and postnasal drip), non-nasal symptoms (individually for eye symptoms, throat symptoms, chronic cough, ear symptoms, headache and mental function), global assessment of overall nasal and non-nasal symptoms severity, as well as global quality of life assessment of rhinitis severity. The scale used for assessment of all individual symptom severity is as follows: 1 = none; 2 = between 1 and 3; 3 = mild; 4 = between 3 and 5; 5 = moderately bothersome; 6 = between 5 and 7; 7 = unbearably severe. When assessing the global nasal symptom and global nasal and non-nasal symptoms, a reverse scale from 1 to 7 is employed. In addition, when assessing the global quality of life in this questionnaire, the scale is: 1= Quality of life is terribly affected in terms of sleep disturbance at night and/or impairment of social and/or recreational activities; 2 = Quality of life is affected almost all the time in terms of sleep disturbance at night and/or impairment of social and/or recreational activities; 3 = Quality of life is affected often in terms of sleep disturbance at night and/or impairment of social and/or recreational activities; 4 = Quality of life is affected occasionally but it is tolerable in terms of sleep disturbance at night and/or impairment of social and/or recreational activities; 5 = Quality of life is hardly affected in terms of sleep disturbance at night and/or impairment of social and/or recreational activities; 6 = Quality of life is hardly noticed in terms of sleep disturbance at night and/or impairment of social and/or recreational activities; 7 = Excellent quality of life
in terms of sleep disturbance at night and/or impairment of social and/or recreational activities.

This VAS instrument has been found to correlate well with the severity of rhinitis, as assessed by the ARIA (Bousquet, Combescure, Klossek, Daures, & Bousquet, 2009; Bousquet, Combescure, et al., 2007).

b. VAS ranging from 0 to 10 cm

A VAS ranging from 0 (nasal symptoms, not at all bothersome) to 10cm (nasal symptoms, extremely bothersome) is designed to assess the severity of combined nasal symptoms (Bousquet, Van Cauwenberge, & Khaltaev, 2001) (Figure 6).

![Figure 6: Visual analogue scale](image)

This simple method was validated to be used for the quantitative evaluation of severity of AR (Bousquet, Combescure, et al., 2007).

### 2.10.2 Questionnaires for assessing quality of life

Quality of life is a complicated concept and can be affected by many factors such as finances, spirituality and health. Health-related quality of life is defined as the part of quality of life being affected by the person’s health condition and that can be affected by clinical management (Juniper et al., 2005). There are several different outcome measures that have been used to assess the AR related quality of life in clinical studies.
2.10.2.1 Generic quality of life questionnaires

Generic quality of life questionnaires such as the Short Form (36) Health Survey (SF-36) (Stewart, Hays, & Ware, 1988) are designed for assessing the health of patients with all kinds of medical conditions. SF-36 contains 36 items, in eight domains about patients’ physical and mental functions. The eight domains are:

- Physical functioning, limitations in physical activities due to health problems;
- Social functioning, limitations in social activities because of physical or emotional problems;
- Role physical limitations in usual role activities because of health problems;
- Bodily pain;
- Mental health, general emotional health (psychological distress and well-being);
- Role emotional, limitations in usual role activities because of emotional problems;
- Vitality (energy and fatigue); and
- General health perceptions.

Although the SF-36 is not a disease specific questionnaire, it is commonly used in health economics as a variable in the quality-adjusted life year (QALY) calculation to determine the cost-effectiveness of a health treatment. Recently, it was employed in a large size cost-effectiveness study of acupuncture for AR (Witt, Reinhold, Jena, Brinkhaus, & Willich, 2009).

2.10.2.2 Specific quality of life questionnaires

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was designed to evaluate patients’ quality of life impairment by the specific condition of AR. This questionnaire contains 28 questions covering 7 domains: activities, sleep, non-
nose/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotional problems. Participants are required to score the questions using a 7 point scale: 0= not troubled; 1= hardly troubled at all; 2= somewhat troubled; 3= moderately troubled; 4= quite a bit troubled; 5= very troubled; 6= extremely troubled (Juniper & Guyatt, 1991). The Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) (Juniper, Thompson, Ferrie, & Roberts, 1999) is an updated version of RQLQ. In the activities domain, instead of letting patients select their own activities, in RQLQ(S), three questions about activities are defined as “regular activities at home and at work”, “social activities” and “outdoor activities”. The RQLQ(S) has been regarded as a more responsive instrument for measuring health related quality of life in rhinitis patients than other generic instruments (Juniper et al., 2005). The Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) is an abbreviated version of RQLQ, with 14 questions in 5 domains (activity limitations, practical problems, nose symptoms, eye symptoms, and other symptoms) (Juniper, Thompson, Ferrie, & Roberts, 2000).

2.10.3 Other assessment

Besides symptoms and quality of life assessment, other measurements are also included in clinical management or clinical research of AR, such as measurements of nasal obstruction, measurements of inflammation, reactivity measurements and measurements of the sense of smell (Juniper et al., 2005).
Chapter 3: Literature review on allergic rhinitis from Chinese medicine perspective

Chinese medicine originated in ancient China and consists of a range of traditional medical practices such as CHM and acupuncture. The earliest practice of acupuncture may date back to the Stone Age based on the discovery of ancient stone needles (Chiu, 1993). The earliest and most fundamental Chinese medicine text, published during the Spring and Autumn period (300-100 BC), is Huangdi’s Internal Classic (Huangdi Neijing). Further progress was made in the Eastern Han Dynasty (150-219 BC) when the Treatise on Cold-Attack and Miscellaneous Diseases (Shang Han Za Bing Lun) written by Zhang Zhong Jing strengthened the traditional Chinese medicine theoretical system. Chinese medicine steadily developed over subsequent centuries (Cheng, 1999). Since the late 20th century, Chinese medicine has been enhanced through systematisation and research of the basic theories of Chinese medicine in combination with the application of modern science and technology to further develop both theory and practice (Zhu & Woerdenbag, 1995). In Western countries Chinese medicine is regarded as part of CAM and has been widely used in many countries including Australia (Xue et al., 2008).

This chapter briefly introduces the fundamental theory of Chinese medicine and the understanding of AR according to Chinese medicine concepts. It also reviews the current clinical research on CHM and acupuncture for treating AR. Ear-acupuncture/ear-acupressure is a subtype of acupuncture. The treatment methods and current research on ear-acupuncture/ear-acupressure for AR will be detailed separately in Chapter 4.
3.1 The fundamental theory of Chinese medicine

Unlike Western medicine, Chinese medicine was developed based on ancient Chinese philosophical framework of *Yin and Yang*, and the *Five-Elements* theory. *Yin and Yang*, and the *Five-Elements* theory were concepts derived from the observation of nature and they were fundamental to all natural sciences in ancient China (Wiseman, 1996). Other key concepts of Chinese medicine include the classification of organs into *Zang and Fu organs* (solid organs and hollow organs or bowels); bodily substances into *Qi, Blood, Fluid and Humour*, and the *Meridian* theory that forms the basis of acupuncture (Cheng, 1999; B. Zhu & Wang, 2010). The following sections introduce the key concepts of CM fundamental theory and the treatment principles.

3.1.1 Key concepts of Chinese medicine theory

3.1.1.1 Yin and Yang

The *Yin* and *Yang* concept represents the two opposite aspects within natural phenomena. This theory was first mentioned in the *Book of Changes (Yi Jing)* in about 700 BC. *Yin* was classified on the basis of having the characteristics of darkness, descending, inward, coldness and stillness whilst *Yang* was classified as having the opposite characteristic of brightness, ascending, outward, heat and movement. *Yin* and *Yang* are two stages of a cyclical movement, one constantly changing into the other, such as the day giving way to night and vice versa. *Yin* and *Yang* can represent not only two opposite objects but also two opposite states of one thing. These two states are not independent of each other and they change into each other. *Yin* and *Yang* are in a constant state of change, so that when one increases the other is consumed, to keep the balance.
The balance between these two forces maintains the normal physiological functions of the human body. Conversely, if either of these two sides becomes excessive or deficient, the human body will lose its balance and become dysfunctional leading to a disease state. Chinese medicine treatments therefore focus on rebalancing Yin and Yang by reinforcing deficiency and reducing excess in order to restore normal human physiological functions in one or more parts or systems (Cheng, 1999; B. Zhu & Wang, 2010).

3.1.1.2 Five-Elements theory

Together with Yin-Yang theory, the Five-Elements theory constitutes the basis of Chinese medicine theory. Basically, the Five-Elements are Wood, Fire, Earth, Metal and Water symbolising five different inherent qualities and states of natural phenomena. The Five-Elements are not independent, each element inter-promotes another and also restrains another following certain sequences. Five-Elements may also overwhelm or rebel against each other when one element is extremely strong.

Five-Elements theory is mainly applied to analyse and study the characteristics of the human organs and their associated tissues and meridians based on a series of correspondences with the basic properties of the Five-Elements. It also explains the physiological functions of the organs, meridians and their interconnections by applying the inter-promotion and restraining relationships of Five-Elements as well as their pathological changes by applying the overacting and counteracting relationships. By combining the Five-Elements theory with Yin-Yang theory and the Zang-Fu organs theory, a model of a functioning human being’s body can be created which helps to explain the mechanisms of health and disease and the diagnosis of clinical disorders (Cheng, 1999; B. Zhu & Wang, 2010).
3.1.1.3 Vital substances (Qi, Blood, Fluid and Humour)

The understanding of the human body’s function also relies on the vital substances inside the body. Qi is the vital energy in the human body which performs the normal physiological functions including movement, warming, defense and transformation. Blood maintains vital activity through its nourishing and moistening functions. Fluid and Humour (Jin and Ye) are the bodily fluids within Zang-Fu organs, the tissues and the normal secretions. The main functions of Fluid and Humour (Jin and Ye) are moistening and nourishing (Cheng, 1999; B. Zhu & Wang, 2010).

3.1.1.4 Meridian system

According to Chinese medicine theory, all Zang-Fu organs and associated structures of the body are connected by the Meridian system, which is also known as the Channels and Collaterals (jing-luo). Also, the organs of the body can be influenced via the Meridian system. This theory is a major component of Chinese medicine and forms the basis of acupuncture treatment. Meridians are the pathways throughout the whole body, through which the Blood and Qi that support life functions flow. These channels are not analogous to any tangible channel in the human body in Western medicine, they are more invisible rather than visible (Liu, Vian, & Eckman, 1998).

All the meridians form a network in which the Qi and Blood circulate. The Qi and Blood flowing in these meridians control and regulate every part of the body. The main trunks of the meridian system are the twelve Regular meridians. Among the twelve Regular meridians, each meridian is associated with either a Zang or a Fu organ and they contain acupuncture points along their length (Cheng, 1999; B. Zhu & Wang, 2010).
3.1.2 Occurrence of disease and treatment principles of CM

The breakdown of the different levels of normal physiological activities (such as the disturbance of Zang-Fu organs and meridians, balance of Yin and Yang, Qi and Blood etc.) results in various clinical manifestations. The factors causing the disequilibrium are termed aetiological factors. These factors include the Six External Excessive pathogenic factors (Wind, Cold, Dryness, Dampness, Summer Heat and Fire Heat), the Seven Excessive Emotions (Anger, Overjoy, Anxiety, Worry, Grief, Fright and Apprehension) and non-internal non-external factors (such as parasites, insect or animal bites, trauma, improper diet, excessive sexual activity, fatigue or lack of exercise), as well as secondary pathological products (such as blood stagnation and phlegm-fluid retention). Any of the above factors can cause imbalance of Yin and Yang and affect the functions of various organs or meridians (Wiseman, 1996).

The main target of Chinese medicine treatment is to reinforce the anti-pathogenic Qi and eliminate the pathogenic factor. Therefore, based on the differentiation of syndromes, the main Chinese medicine therapeutic principles include (Wiseman, 1996):

- Treating the primary cause and the secondary aspect of a disease;
- Reinforcing the healthy Qi and eliminating the pathogenic factor;
- Regulating Yin and Yang;
- Regulating the functions of the Zang and Fu organs;
- Regulating the relationship between Qi and Blood; and
- Treating a disease according to season, environment and individual constitution.
The next section will introduce AR from the Chinese medicine perspective based on the understanding of the fundamental theory of Chinese medicine.

3.2 AR in Chinese medicine

AR is a specific concept in Chinese medicine in regard to its definition, aetiology and pathogenesis, differential diagnosis and treatment.

3.2.1 Definition of AR in Chinese medicine

AR is the medical term for a Western medicine category. However, in Chinese medicine, there is no single condition that matches all the symptoms of AR. The most similar disease in Chinese medicine is “Bi Qiu 鼻鼽” (Wang & Gan, 1985). Bi refers to the nose and Qiu means clear rhinorrhea. Qiu also refers to Qiu Ti 鼻嚏 and Qiu Shui 鼻水. Ti is sneezing and Shui means discharge. Therefore, the term Bi Qiu 鼻鼽 covers the symptoms of sneezing and runny nose, which are the major symptoms of AR (Wang & Gan, 1985).

A condition with clear nasal discharge was first documented in the literature in the 11th Century BC (Xizhou Dynasty), and the description was further developed in the text Huangdi’s Internal Classic (Huangdi Neijing) between 475 to 221 BC; In 610 AD, the physician Chao Yuan Fang explained that excessive nasal discharge was caused by deficiency of Fei (Lung) Qi combining with cold pathogens. Liu Wan Su (1182 to 1209) clarified that symptoms such as rhinorrhea, itchy nose and sneezing were the result of Fei (Lung) Qi deficiency in the book titled The Pattern and Mechanism of Causation of Diseases from Basic Questions (Su Wen Xuan Ji Yuan Bing Shi). In 1249, Li Dong Yuan concluded that deficiency of the Pi (Spleen) and Wei (Stomach)
was also related to these symptoms according to the theory of *Five-Phases* in *Comments on Spleen and Stomach (Piwei Lun)*. Furthermore, Chinese medicine described this condition's occurrence as induced by the invasion of *Wind-cold* (Wang & Gan, 1985).

### 3.2.2 Aetiology and pathogenesis of AR in Chinese medicine

According to Chinese medicine theory, respiration is dominated by the *Fei* (Lung) organ. The concept of *Fei* (Lung) in Chinese medicine is similar to the lungs in western medicine but it is much broader than the anatomical lungs since it includes the nose and skin. *Fei* (Lung)’s main role is performing respiration, dominating the function of dispersion and depuration, descending *Qi* and regulating both *Qi* activity and the metabolism of *Body Fluid*. The *Fei* (Lung) *Qi* controls the defensive *Qi* which is distributed to the body surface to protect it from attack by external factors. *Fei* (Lung) has a close relationship with the nose. *Fei* (Lung) opens into the nose and the nose is the portal of *Fei* (Lung). If *Fei* (Lung) *Qi* is harmonised, the nose will be unobstructed, the respiration will be smooth and the sense of smell will be acute. Once the *Fei* (Lung) is attacked by pathogenic factors, it will fail to disperse and regulate the *Body Fluid*, therefore, symptoms like nasal obstruction, watery nose and decrease in smell sensation will occur (Maciocia, 2005). In addition, *Pi* (Spleen) and *Shen* (Kidney) also play an important role in AR due to their functions associated with *Qi*. When *Pi* (Spleen/digestive system) *Qi* is impaired, *Fei* (Lung) *Qi* will be deficient as a result of losing aid from *Pi* (Spleen) *Qi*. When *Shen* (Kidney) does not store the essence of *Qi* properly, *Fei* (Lung) will lose the function of governing *Qi* (Maciocia, 2005).
The occurrence of Bi Qiu is due to the invasion of the exterior pathogen Wind-cold and is associated with deficiency of Fei (Lung) Qi, Pi (Spleen) Qi and/or Shen (Kidney) Qi. Wind-cold is the external pathogen which invades the body while the deficiency of Qi represents the failure of internal factors to repel the invasion. Wind-cold invasion is similar to the inhalation of an allergen while deficiency of Qi is similar to dysfunction of the immune system in the western medicine view (Maciocia, 2005).

When the defence Qi is weak, the pathogenic Wind-cold can invade the body and cause a loss of balance between Yin and Yang leading to a disease state characterised by either Fei (Lung) Qi, Pi (Spleen) Qi and/or Shen (Kidney) Qi deficiency (Maciocia, 2005).

3.2.2.1 Fei (Lung) Qi deficiency

Fei (Lung) Qi is the reflection of the overall function of the Fei (Lung). Fei (Lung) Qi is originally produced by the Shen (Kidney) and constantly replenished by the Pi (Spleen). When the Fei (Lung) Qi is over consumed due to long-term cough, congenital deficiency or insufficient provision from the digestive system (Pi Wei, Spleen & Stomach), the Fei (Lung) and its associated structures (the nose and skin) will be susceptible to invasion by pathogenic factors. Wind-cold is one pathogenic factor that easily invades the human body through the nose and the mouth. Sneezing is due to the invasion of Cold while itchiness in nose, eye and throat is the symptom caused by the Wind. When the impaired Fei (Lung) Qi fails to maintain the normal function of the nasal passages and the water metabolism, nasal blockage and watery rhinorrhoea will occur (Maciocia, 2005).
3.2.2.2 Pi (Spleen) Qi deficiency

In Chinese medicine, Pi (Spleen) and Wei (Stomach) refer to the digestive system and are described as the postnatal foundation of life which provides all the nutrients to the entire body. The Pi (Spleen) Qi may be impaired if the person is under stress, suffering from overthinking and/or imbalanced diet. In addition, dysfunction of other organs such as the Gan (Liver) and Shen (Kidney) may also indirectly affect the Pi (Spleen) function. Once the Pi (Spleen) Qi is deficient, it is not able to generate adequate nutrients to replenish the Fei (Lung) Qi and this can cause Fei (Lung) Qi deficiency. It will also affect the water metabolism due to dysfunction in its role of distributing Body Fluid, so that rhinitis symptoms can occur (Maciocia, 2005).

3.2.2.3 Shen (Kidney) Qi deficiency

According to the Chinese medicine theory, the Shen (Kidney) is the congenital foundation for the entire body in relation to its function of providing the primary Qi at conception and birth. Furthermore, the Shen (Kidney) has the function of warming and nourishing the Pi (Spleen). It also has a close relationship with Fei (Lung) function in order to descend the Qi derived from breathing and thereby maintain the proper functioning of the respiratory tracts. Via its control over urination Shen (Kidney) has an important role in balancing water metabolism. Therefore, when the Shen (Kidney) Qi is deficient, Fei (Lung) and Pi (Spleen) may not be able to function well and this may contribute to rhinitis symptoms (Maciocia, 2005).

The aetiology and pathogenesis of AR in Chinese medicine is illustrated in the Figure 7.
Figure 7: Aetiology and pathogenesis of AR in Chinese medicine

3.2.3 Differential diagnosis of AR in Chinese medicine

Based on its aetiology and pathogenesis, Bi Qiu can be clustered as three syndromes: Fei (Lung) Qi deficiency, Pi (Spleen) Qi deficiency and Shen (Kidney) Qi deficiency. Table 3 provides a summary of the AR symptom differentiation in Chinese medicine (Maciocia, 2005).
### Table 3: Chinese medicine differential diagnosis of AR

<table>
<thead>
<tr>
<th></th>
<th>Key symptoms</th>
<th>Tongue</th>
<th>Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common symptoms</strong></td>
<td>Sudden onset of continuous sneezing, nose itch, watery rhinorrhoea and nasal congestion may be associated with impairment of smell, eye itch and itchy palate.</td>
<td>Pale tongue and white coating</td>
<td>Superficial &amp; weak</td>
</tr>
<tr>
<td><strong>Fei (Lung) Qi deficiency</strong></td>
<td>Easily catches cold, spontaneously sweats and reduced sense of smell</td>
<td>Pale tongue or enlarged with teeth marks, white coating</td>
<td>Weak &amp; thready</td>
</tr>
<tr>
<td><strong>Pi (Spleen) Qi deficiency</strong></td>
<td>Heavy-headed, tired or exhausted, heavy limbs, loss of appetite and loose bowels</td>
<td>Pale tongue or enlarged with teeth marks, white coating</td>
<td>Weak &amp; thready</td>
</tr>
<tr>
<td><strong>Shen (Kidney) Qi deficiency</strong></td>
<td>Cold limbs, weakness in the lumbar area and knees, frequent nocturnal urination and shortness of breath after light physical exercise</td>
<td>Pale tongue with white coating</td>
<td>Deep &amp; weak</td>
</tr>
</tbody>
</table>

#### 3.3 CHM and acupuncture management for AR

The principle of Chinese medicine treatment is based on the diagnosis, which determines the nature of a condition as deficiency or excess. The aim of treatment is to restore the balance of Qi and Blood, Yin and Yang, and the Zang-Fu organs.

Tonification means using an enhancing and strengthening method for treating deficient syndromes. Reduction means the elimination and dispelling of excessive pathogens. Therefore, warming the Fei (Lung) and dispelling Cold is the principle of treatment for the Wind-cold syndrome; tonifying Fei (Lung) Qi to strengthen the superficial resistance is for the treatment of Fei (Lung) Qi deficiency; strengthening Pi (Spleen) Qi to supplement Qi is the treatment principle for Pi (Spleen) Qi deficiency; and tonifying the Shen (Kidney) to promote Qi is the treatment principle for Shen (Kidney) Qi deficiency (Maciocia, 2005).
CHM and acupuncture are the commonly used modalities of Chinese medicine. This section introduces the CHM and acupuncture treatment for AR and current clinical research in this area.

### 3.3.1 CHM for AR

Based on Chinese medicine theory, Chinese herbs have characters of five *Flavours* and four *Energies*. Five *Flavours* in nature are *Sour*, *Bitter*, *Sweet*, *Pungent* and *Salty* and the *Four Energies* are *Cold*, *Hot*, *Warm* and *Cool*. The five *Flavours* are related to the *Five-Zang Organs* through their association with the *Five-Elements*. The function of four *Energies* is to work on the nature of the imbalance, for example *Warm* and *Hot* can warm the *Yang*, while *Cold* and *Cool* can clear the *Heat*, and flush out the *Fire*. Each CHM has specific functions based on its *Flavour* and *Energies*. Using the proper CHMs according to the differential diagnosis will restore balance to the functioning of the relevant organs (Maciocia, 2005).

In clinical practice, CHM formulas can be chosen according to the differential diagnosis of patients’ syndrome. The selection of CHM formulations is based on the traditional therapeutic effects of the individual herbal medicines and the interaction among the various herbal substances. An individualised treatment plan can be provided through modifying the formulas. The CHM formulas related to AR treatment are summarised in Table 4 (Liu, 1988).
Table 4: CHM formulas and individual herbs for AR

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Treatment principle</th>
<th>Formula</th>
<th>Herbal medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fei (Lung) Qi deficiency</td>
<td>Tonify Fei (Lung) Qi and strengthen the superficial resistance</td>
<td>Yu Ping Feng San</td>
<td>Huang Qi (Radix Astragali seu Hedysari)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fang Feng (Saposhnikvia divaricata)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bai Zhu (Rhizoma Atractylodis Macrocephalae)</td>
</tr>
<tr>
<td>Pi (Spleen) Qi deficiency</td>
<td>Nourish Pi (Spleen) and benefit Fei (Lung)</td>
<td>Bu Zhong Yi Qi Tang</td>
<td>Huang Qi (Radix Astragali seu Hedysari)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Zhi Gan Cao (Radix Glycyrrhizae Preparata)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ren Shen (Radix Ginseng)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chen Pi (Pericarpium Citri Reticulatae)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sheng Ma (Rhizoma Cimicifugae)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chai Hu (Radix Bupleuri)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bai Zhu (Rhizoma Atractylodis Macrocephalae)</td>
</tr>
<tr>
<td>Shen (Kidney) Qi deficiency</td>
<td>Tonify Shen (Kidney)</td>
<td>Jin Gui Shen Qi Wan</td>
<td>Shu Di (Radix Rehmaniae Praeparata)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shan Yao (Rhizoma Dioscoreae)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shan Zhu Yu (Fructus Corni)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fu Ling (Poria)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ze Xie (Rhizoma Alismatis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dan Pi (Cortex Moutan Radicis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fu Zi (Radix Aconiti Praeparata)</td>
</tr>
</tbody>
</table>

3.3.2 Acupuncture for AR

Acupuncture is a technique that involves inserting metal needles into certain points of the human body. The mechanism of acupuncture is based on the meridian theory of Chinese medicine. This method has been used in clinical practice for thousands of years.

The practice of acupuncture can perhaps be traced as far back as the Stone Age (approximately three million years ago), with the *Bian shi*, or sharpened stones being used in ancient China. The fact that stimulating certain points on the body could relieve pain or other illnesses was observed, then people started to discover the relationships between internal parts and external parts of the human body and eventually formed the meridian theory (Cheng, 1999).
The earliest available written record about acupuncture is Huangdi’s Internal Classic (*Huangdi Neijing*), which was compiled around 475–221 BC. The technique of acupuncture was applied using different types of needles or instruments to stimulate certain points. By activating the circulation of *Qi* and *Blood* in the flow of the meridian system, the physiological function of the human body could be adjusted and diseases could be cured.

During thousands of years of clinical practice, the acupuncture system played an important role in the clinical diagnosis and management of a variety of conditions (Cheng, 1999). Acupuncture has been adopted by western societies such as Australia as one of the most popular treatments of the CAM therapies (Xue et al., 2008).

In the treatment for AR with acupuncture, the principles of tonifying the deficient *Fei* (Lung), *Pi* (Spleen) or *Shen* (Kidney) and eliminating the *Wind* and *Cold* are applied through selecting relevant points and using manipulation techniques during the treatment process (Table 5) (Liu, 1988).
Table 5: Acupuncture points selection for AR

<table>
<thead>
<tr>
<th>Treatment principle</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local points around the nose area</td>
<td>Yingxiang (LI 20), Kouheliao (LI 19)</td>
</tr>
<tr>
<td>To tonify the <em>Fei</em> (Lung) <em>Qi</em></td>
<td>Taiyuan (LU 9)</td>
</tr>
<tr>
<td>To tonify the <em>Pi</em> (Spleen) <em>Qi</em></td>
<td>Zusanli (ST 36)</td>
</tr>
<tr>
<td>To tonify the <em>Shen</em> (Kidney)</td>
<td>Taixi (KI 3)</td>
</tr>
<tr>
<td>To eliminate the <em>Wind</em> and <em>Cold</em></td>
<td>Fengchi (GB 20)</td>
</tr>
</tbody>
</table>

Similar to the CHMs for treating AR, the acupuncture points for AR should be selected by following the principles listed in the table above and can be combined or modified according to the differential diagnosis.

In fact, the Chinese medicine treatments mainly rely on experience and empiricism handed down from generation to generation. The knowledge and experience in both CHM and acupuncture have accumulated over centuries of practice and clinical observations. However, from a research methodological point of view, more scientific evidence is needed to substantiate the claim of the clinical benefit. Therefore, a critical review of the clinical trial literature for CHM and acupuncture was carried out in order to obtain a clearer picture regarding the current state of the clinical research in the area of CHM and acupuncture and their roles in the clinical management of AR.

3.4 Existing reviews on CHM and acupuncture for AR

The number of RCTs on CHM and acupuncture has increased significantly in recent years (Xue, Zhang, Greenwood, Lin, & Story, 2010). In the field of CHM and acupuncture for AR, some systematic reviews and overviews of RCTs have been conducted to evaluate the current evidence (Guo, Pittler, & Ernst, 2007; Lee, Pittler, Shin, Kim, & Ernst, 2009; Roberts, Huissoon, Dretzke, Wang, & Hyde, 2008; Witt &
In order to define the clinical effectiveness and safety of CHM and acupuncture for AR, this section reviews and summarises all the RCTs included in current existing systematic reviews and overviews.

Literature search was carried out in the following databases: Pubmed, Embase, and Cochrane Library from their inceptions to April 2008 and updated in January 2011. Search terms used were: allergic rhinitis, Chinese herbal medicine, herbal medicine, acupuncture, complementary and alternative medicine, randomised controlled trial, systematic review, overview, meta-analysis. Systematic reviews (including or not including meta-analysis) or overviews of RCTs of all types of CAM therapies for AR were included. Only the RCTs of CHM and acupuncture for AR published in the language of English were extracted from the included RCTs. As a result of the search, five systematic reviews and overviews on the RCTs of CHM and acupuncture (Lee, Pittler, Shin, Kim, & Ernst, 2009; Roberts, Huissoon, Dretzke, Wang, & Hyde, 2008; Witt & Brinkhaus, 2010), herbal medicine (Guo, Pittler, & Ernst, 2007), and CAM therapies (Passalacqua et al., 2006) for AR were considered, and their included RCTs are reviewed in this section. Study selection procedure is summarised in Figure 8.
Two RCTs of CHM for AR (Hu et al., 2002; Xue et al., 2003), nine RCTs of acupuncture for AR (Brinkhaus et al., 2008; Y. M. Li, Zhuang, Lai, & Jiang, 2007; Magnusson, Svensson, Leirvik, & Gunnarsson, 2004; Ng et al., 2004; Petti, Liguori, & Ippoliti, 2002; Rao & Han, 2006; Williamson et al., 1996; Xue, English, Zhang, Da Costa, & Li, 2002; Xue et al., 2007) and one RCT (Brinkhaus et al., 2004) of the combination of CHM and acupuncture for AR were included and extracted. Details are listed in Table 6 below.
<table>
<thead>
<tr>
<th>Review</th>
<th>Review focus and included studies (n=)</th>
<th>RCTs extracted from included reviews</th>
<th>Reviewer’s comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo 2007</td>
<td>Systematic review on herbal medicine for AR (n=16)</td>
<td>Hu 2002, Xue 2003</td>
<td>All RCTs on CHM for AR generated positive results.</td>
</tr>
<tr>
<td>Robert 2008</td>
<td>Systematic review on acupuncture for AR (n=7)</td>
<td>Williamson 1996, Petti 2002, Xue 2002, Ng 2004, Magnusson 2004,</td>
<td>Meta-analysis failed to show any summary benefits of acupuncture for AR.</td>
</tr>
<tr>
<td>Lee 2009</td>
<td>Systematic review on acupuncture for AR (n=12)</td>
<td>Williamson 1996, Petti 2002, Xue 2002, Ng 2004, Magnusson 2004, Rao 2006, Xue 2007</td>
<td>No specific effects of acupuncture SAR; suggestive evidence of acupuncture for PAR was provided.</td>
</tr>
</tbody>
</table>
All these RCTs were summarised with regard to methodological quality, intervention/control method, efficacy and safety.

The Jadad scale (Jadad et al., 1996) was used to assess the methodological quality of included studies as it was commonly employed in these reviews for methodological quality assessment (Guo, Pittler, & Ernst, 2007; Lee, Pittler, Shin, Kim, & Ernst, 2009; Passalacqua et al., 2006; Roberts, Huissoon, Dretzke, Wang, & Hyde, 2008). This is a six-point scale that assesses methodological quality of clinical trials with respect to randomisation, blinding and dropouts/withdrawals. The scoring method is as follows: if the study describes details of randomisation, blinding and methods dealing with withdrawals, one point is given to each of the three items. If the randomisation method is appropriate and the blinding is adequate, one additional point is allocated to each of the above two items. However, if a study has inappropriate randomisation and/or inadequate blinding, one point is deducted for each of these two items (Jadad et al., 1996).

All included studies are categorised in three groups: CHM for AR, acupuncture for AR and acupuncture combined with CHM for AR (sections 3.4.1 to 3.4.3).

### 3.4.1 CHM for AR

Two studies (Hu et al., 2002; Xue et al., 2003) that focused on CHM for AR were included in this category. They were both conducted in Australia and published in English. The sample size of these two studies is small: 55 (Xue et al., 2003) and 58 (Hu et al., 2002). Conditions treated in these two studies are SAR (Xue et al., 2003) and PAR (Hu et al., 2002). When assessing the methodological quality of these two studies with the 6 point (0 to 5) Jadad scale, they both were assessed as high quality...
RCTs (Jadad score 5). The characteristics of these two RCTs are summarised in Table 7.
Table 7: Characteristics of the two included RCTs (CHM for AR)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Condition</th>
<th>Analysed Sample Size (Groups T/C)</th>
<th>Treatment duration</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xue 2003</td>
<td>Australia</td>
<td>SAR</td>
<td>55 (28/27)</td>
<td>8 weeks</td>
<td>CHM in capsules, made from 18 Chinese medicine herbs</td>
<td>Placebo capsules</td>
<td>Nasal and non-nasal symptoms score, RQLQ, overall individual response to treatment, relief medication score, patients’ opinion and blood tests.</td>
<td>T&gt;C, p&lt;0.01</td>
<td>5</td>
</tr>
<tr>
<td>Hu 2002</td>
<td>Australia</td>
<td>PAR</td>
<td>58 (26/32)</td>
<td>12 weeks</td>
<td><em>Biminne</em> in capsules, made from 11 Chinese medicine herbs</td>
<td>Placebo capsules</td>
<td>Symptoms score, QOL, patients’ evaluation of improvement VAS, physician’s overall evaluation, total serum IgE</td>
<td>T&gt;C, p&lt;0.05</td>
<td>5</td>
</tr>
</tbody>
</table>

Notes: PAR: perennial allergic rhinitis; SAR: seasonal allergic rhinitis; T: treatment group; C: control group.
Both of these studies used capsules made from CHM formulas extraction as the intervention with placebo capsules as the control. The formula used in Xue (2003) study included 18 Chinese herbs (Dang Gui, Xi Xin, Huang Qi, Bai Zhu, Chai Hu, Sheng Ma, Dang Shen, Gan Cao, Chuan Xiong, Xin Yi, Bo He, Chen Pi, Che Qian Zi, Wu Wei Zi, Jing Jie, Fang Feng, He Zi, Cang Er Zi) while that in Hu (2002) study included 11 Chinese herbs (Di Huang, Huang Qin, Huang Jing, Yin Xing Ye, Yin Yang Huo, Bu Gu Zhi, Wu Wei Zi, Wu Mei, Fang Feng, Bai Zi, Huang Qi). Treatment duration was eight weeks (Xue et al., 2003) and 12 weeks (Hu et al., 2002). Both studies employed similar outcome measures such as symptom scores, quality of life assessment and blood tests. In addition, Xue (2003) also included a relief medication score as an outcome measure.

In terms of efficacy, both studies reported that the specific CHM formula was more effective compared with placebo in reducing the symptom severity and in improving patients’ quality of life. In the study by Xue (2003), no significant difference was found in the relief medication score between the CHM and placebo groups. However, this may have been caused by the variety of medications used for AR symptoms (Xue et al., 2003). Due to multiplicity of herbs involved in these two studies, a firm conclusion regarding to the efficacy of CHM in the clinical management of AR could not be drawn.

With regard to the safety of CHM for AR, one study (Xue et al., 2003) reported some mild gastrointestinal side effects such as bloating, indigestion and mild stomach-ache by the patients in both groups. These mild discomforts were tolerable and did not require medical treatment. Another adverse event reported in this study was skin rash and leg oedema from the real treatment group which required medical attention.
and led to withdrawal from the study. However, it is not clear whether these gastrointestinal discomforts were caused by certain herbs in the formula or the intake of 12 capsules per day (Xue et al., 2003). The other study (Hu et al., 2002) reported two adverse events (stomach upset and dull abdominal pain) involving two patients in the placebo group, which led these two patients to withdraw from the trial.

### 3.4.2 Acupuncture for AR

Nine studies (Brinkhaus et al., 2008; Li, Zhuang, Lai, & Jiang, 2007; Magnusson, Svensson, Leirvik, & Gunnarsson, 2004; Ng et al., 2004; Petti, Liguori, & Ippoliti, 2002; Rao & Han, 2006; Williamson et al., 1996; Xue, English, Zhang, Da Costa, & Li, 2002; Xue et al., 2007) focussing on acupuncture for AR were extracted from the identified reviews. They were conducted in Europe (Germany, Sweden, and Italy), Australia, mainland China and Hong Kong. The sample size of these studies varied from 20 to over 981. Conditions treated in these studies included SAR (Magnusson, Svensson, Leirvik, & Gunnarsson, 2004; Xue, English, Zhang, Da Costa, & Li, 2002), PAR (Li, Zhuang, Lai, & Jiang, 2007; Petti, Liguori, & Ippoliti, 2002), SAR and/or PAR (Brinkhaus et al., 2008) or PER (Ng et al., 2004; Xue et al., 2007). However, two studies did not specify the classification of AR (Rao & Han, 2006; Williamson et al., 1996). In fact, the study by Williamson (1996) mentioned the “hay fever season”, hence it seems that this study was targeting SAR patients. The characteristics of these RCTs are summarised in Table 8.
Table 8: Characteristics of the nine included RCTs (Acupuncture for AR)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Condition</th>
<th>Analysed Sample Size (Groups T/C)</th>
<th>Treatment duration</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brinkhaus 2008</td>
<td>Germany</td>
<td>SAR and/or PAR</td>
<td>981 (487/494)</td>
<td>3 months</td>
<td>Usual care plus acupuncture 10 sessions</td>
<td>Usual care alone</td>
<td>Cost; SF-36; QALYs</td>
<td>T&gt;C, p&lt;0.001</td>
<td>3</td>
</tr>
<tr>
<td>Xue 2007</td>
<td>Australia</td>
<td>PER</td>
<td>80 (42/38)</td>
<td>8 weeks treatment, 12 weeks follow-up</td>
<td>Acupuncture 16 sessions</td>
<td>Sham acupuncture 16 sessions</td>
<td>Daily nasal symptoms score; weekly symptom score and total nasal symptom scores (TNSS); seven-day relief medication scores</td>
<td>T&gt;C, short-term and long-term p=0.001, 0.02</td>
<td>4</td>
</tr>
<tr>
<td>Li 2007</td>
<td>China</td>
<td>PAR</td>
<td>100 (50/50)</td>
<td>30 days</td>
<td>Electro-acupuncture, 30 sessions</td>
<td>Cetirizine</td>
<td>Percentage of effectiveness based on symptom score; plasma vasoactive intestinal peptide, substance P</td>
<td>T&gt;C, p&lt;0.05</td>
<td>1</td>
</tr>
<tr>
<td>Rao 2006</td>
<td>China</td>
<td>AR</td>
<td>93 (47/46)</td>
<td>28 days treatment, 6 months follow-up</td>
<td>Acupuncture, 24 sessions</td>
<td>Cetirizine</td>
<td>Symptom score. serum total IgE, IFN-r, IL-4</td>
<td>T&gt;C, long term only, p&lt;0.05</td>
<td>2</td>
</tr>
<tr>
<td>Ng 2004</td>
<td>Hong Kong, China</td>
<td>PER</td>
<td>72 (35/37)</td>
<td>8 weeks treatment, 12 weeks follow-up</td>
<td>Acupuncture 16 sessions</td>
<td>Sham acupuncture 16 sessions</td>
<td>Daily rhinitis scores, Symptom-free days. VAS score for immediate improvement after acupuncture; Relief medication score; Treatment preferences of participants; Blood eosinophil counts; Nasal eosinophil counts; Serum IgE levels</td>
<td>T&gt;C, short-term and long-term, p&lt;0.05</td>
<td>5</td>
</tr>
<tr>
<td>Magnusson 2004</td>
<td>Sweden</td>
<td>SAR</td>
<td>32 (14/18)</td>
<td>3 months treatment, 12 months follow-up</td>
<td>Acupuncture 12 sessions</td>
<td>Sham acupuncture 12 sessions</td>
<td>Symptoms VAS; Reduction of levels of specific IgE; Reduction in skin test reaction</td>
<td>T&gt;C, short-term, p&lt;0.05</td>
<td>4</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Country</td>
<td>Condition</td>
<td>Analysed Sample Size (Groups T/C)</td>
<td>Treatment duration</td>
<td>Intervention</td>
<td>Control</td>
<td>Outcome measures</td>
<td>Results</td>
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<tr>
<td>Xue 2002</td>
<td>Australia</td>
<td>SAR</td>
<td>30 (17/13)</td>
<td>4 weeks, then cross over</td>
<td>Acupuncture 12 sessions</td>
<td>Sham acupuncture 12 sessions,</td>
<td>Symptom score, relief medication score</td>
<td>T&gt;C, p&lt;0.05</td>
<td>3</td>
</tr>
<tr>
<td>Petti 2002</td>
<td>Italy</td>
<td>PAR</td>
<td>90 (30/30/30)</td>
<td>20 minutes</td>
<td>Acupuncture 1 session</td>
<td>C1: sham acupuncture, C2: no treatment</td>
<td>Cytokines IL-2, IL-6, IL-10</td>
<td>T&gt;C1 and C2, p&lt;0.05</td>
<td>2</td>
</tr>
<tr>
<td>Williamson 1996</td>
<td>UK</td>
<td>“hay fever” SAR</td>
<td>102 (51/51)</td>
<td>one month per year for 3 years</td>
<td>Acupuncture 3 or 4 sessions</td>
<td>Sham acupuncture</td>
<td>Daily symptom score; Medication usage</td>
<td>T&gt;C, p&lt;0.05</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: PAR: perennial allergic rhinitis; SAR: seasonal allergic rhinitis; PER: persistent allergic rhinitis; T: treatment group; C: control group.
Using the 6 point (0 to 5) Jadad scale, four studies (Li, Zhuang, Lai, & Jiang, 2007; Petti, Liguori, & Ippoliti, 2002; Rao & Han, 2006; Williamson et al., 1996) were assessed as low quality (Jadad score 1 or 2) and the other studies (Brinkhaus et al., 2008; Magnusson, Svensson, Leirvik, & Gunnarsson, 2004; Ng et al., 2004; Xue, English, Zhang, Da Costa, & Li, 2002; Xue et al., 2007) were high quality (Jadad score 3 and above).

Among the nine studies, comparing real acupuncture with sham acupuncture is the most frequently used design (Magnusson, Svensson, Leirvik, & Gunnarsson, 2004; Ng et al., 2004; Petti, Liguori, & Ippoliti, 2002; Williamson et al., 1996; Xue, English, Zhang, Da Costa, & Li, 2002; Xue et al., 2007). Other studies compared a combination of acupuncture treatment and usual care with usual care alone (Brinkhaus et al., 2008), or acupuncture treatment versus anti-histamine medication (Li, Zhuang, Lai, & Jiang, 2007; Rao & Han, 2006). Electro-acupuncture was employed as the intervention in one study (Li, Zhuang, Lai, & Jiang, 2007).

When acupuncture was compared with sham acupuncture, one study (Xue, English, Zhang, Da Costa, & Li, 2002) reported that acupuncture was superior for treating SAR by reducing the symptom severity score; one study demonstrated the effectiveness of acupuncture on mean rhinitis symptoms score during the follow-up period for PER patients (Xue et al., 2007); one study showed positive results for acupuncture in PER patients by decreasing the symptom scores and increasing the symptom-free days (Ng et al., 2004); one study (Williamson et al., 1996) reported acupuncture was effective in reducing the weekly symptom score and weekly medication usage; while two studies (Ng et al., 2004; Xue, English, Zhang, Da Costa, & Li, 2002) found that acupuncture was only effective in reducing symptom scores.
but not in reducing medication scores. One study (Magnusson 2004) reported that acupuncture significantly reduced specific IgE and skin test reactions. When acupuncture was compared with oral antihistamine drugs for AR, two RCTs showed favourable effects for acupuncture (Li, Zhuang, Lai, & Jiang, 2007; Rao & Han, 2006). Li (2007) demonstrated that electroacupuncture was more effective than antihistamine (Cetirizine) in terms of the effective rate while Rao (2006) reported that acupuncture had a similar short-term effect to that of antihistamine (Cetirizine) but a better long-term effect.

The outcome measure of relief medication score was used in four studies (Ng et al., 2004; Williamson et al., 1996; Xue, English, Zhang, Da Costa, & Li, 2002; Xue et al., 2007). The results for medication scores from these four studies were not consistent. Only one study (Williamson et al., 1996) reported that lower medication usage was observed in the real group compared with sham group at the end of treatment period. This might be caused by the variety of medications used for AR symptom control and the consequent difficulty in determining a single score.

It is important to note that the large sized RCT of acupuncture for AR (Brinkhaus et al., 2008) also investigated the cost-effectiveness of acupuncture for AR management by assessing the QALYs gained (Witt, Reinhold, Jena, Brinkhaus, & Willich, 2009). It was a part of a series of the Acupuncture in Routine Care studies funded by the German statutory health insurance companies. This study concluded that acupuncture combined with routine care was not only beneficial for AR symptomatic control, but also cost effective.
Acupuncture does not involve any drug. Therefore, the side effects of drugs and pharmacologic interactions can be avoided using this treatment. Some of the studies reported mild adverse events such as pain, bruising, dizziness, numbness and headache caused by the needling technique (Ng et al., 2004; Xue et al., 2007). No serious adverse event was reported, and no withdrawals were attributable to adverse events due to acupuncture.

In summary, based on the included studies on acupuncture for AR, acupuncture seems to be effective for AR symptomatic relief and quality of life improvement.

### 3.4.3 Acupuncture combined with CHM for AR

There is also one study investigating the combination of acupuncture and CHM for the management of AR (Brinkhaus et al., 2004). This study was conducted in Germany (Brinkhaus et al., 2004). Fifty-four SAR participants were included in this study.

The characteristics are summarised in Table 9.

In this study, acupuncture was combined with CHM as the intervention and compared with sham acupuncture plus placebo CHM. A positive result was obtained in this study. However, it is not clear if the effectiveness was caused by acupuncture or CHM.

This study reported adverse events caused by needling such as severe needle pain, haematoma, paraesthesia and bruising from acupuncture; while the adverse events caused by CHM were bloating, indigestion, mild stomach ache, nausea and bitter taste.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Condition</th>
<th>Analysed Sample Size (Groups T/C)</th>
<th>Treatment duration</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brinkhaus 2004</td>
<td>Germany</td>
<td>SAR</td>
<td>54 (28/26)</td>
<td>6 weeks</td>
<td>Semi-standardised treatment of acupuncture, 6 sessions, and CHM for 6 weeks</td>
<td>Acupuncture on non-acupuncture points, 6 sessions, plus non-specific CHM</td>
<td>Global rating of weekly symptom severity; Symptom score, Global assessment of change; RQLQ; SF-36.</td>
<td>T&gt;C, <em>p</em>&lt;0.05</td>
<td>4</td>
</tr>
</tbody>
</table>

Notes: SAR: seasonal allergic rhinitis; T: treatment group; C: control group.
3.4.4 Discussion

In summary, based on the above review of the clinical research in CHM and acupuncture for the management of AR, positive findings from the previous RCTs suggested that CHM and acupuncture are effective for treating AR.

However, the exact mechanism of CHM or acupuncture in treating AR still remains uncertain. Although some laboratory research has studied the pharmacology and immunological action of herbal medicines (Kao, Wang, Wang, Yu, & Lei, 2000; Ko et al., 2004; Lenon, Li, Xue, Thien, & Story, 2007; Lenon, Li, Xue, Thien, & Story, 2008; Lenon et al., 2007; Makino, Ito, Sasaki, Fujimura, & Kano, 2004), a firm conclusion cannot be drawn since the CHM formulas involved in these studies vary greatly from study to study.

In recent years, researchers have conducted a number of animal experiments and clinical trials to investigate the anti-inflammatory effects of acupuncture. It has been reported that electroacupuncture has an impact on the hypothalamus-pituitary-adrenal (HPA) axis by increasing Adrenocorticotropic hormone (ACTH) levels and suppressing oedema (Li et al., 2008), and on nerve pathways such as the sympathetic post-ganglionic neurons and the sympatho-adrenal medullary axis (Kim et al., 2008), as well as on the opioid neuropeptides (Fu, Wang, & Wu, 2006). A recent study suggested that acupuncture is related to the release of adenosine, a neuromodulator with anti-nociceptive properties (Goldman et al., 2010).

Electroacupuncture is believed to elicit and enhance innate immunity and modulate adaptive immune system (Kim, & Bae, 2010). The effects of acupuncture for allergic diseases may rely on the anti-inflammatory effects of acupuncture mediated through
neurotrophins, (Nockher & Renz, 2006), cytokines (Joos, Schott, Zou, Daniel, & Martin, 2000; Petti, Liguori, & Ippoliti, 2002; Rao & Han, 2006), nitric oxide and leukotriene B4 (Carneiro, Xavier, De Castro, Do Nascimento & Silveira, 2010). A recent study on asthmatic rats found that acupuncture could specifically and effectively regulate the early airway response phase of asthma, and suggested that the gene expression of immune response and steroid hormones may play an important role in this treatment (Yin et al., 2009). All these mechanisms of acupuncture are yet to be confirmed.

Furthermore, the safety issue of CHM for AR management needs to be considered. Herbs usually contain active compounds, thus it is not surprising that CHMs have some measurable clinical effects. On the other hand, for the same reason, they are not completely devoid of side effects and pharmacologic interactions (Passalacqua et al., 2006). Some side effects caused by herbal remedies have been reported by other studies (Barrett, Kiefer, & Rabago, 1999; Cupp, 1999). Hence, the safety of herbal medicines is an issue of public concern.

For acupuncture, the therapeutic effects are obtained by stimulation of the acupoints by needling. Being an invasive technique, adverse events such as bruising, pain and others can occur. A recent survey of 229,230 patients who had experienced acupuncture indicated that bleeding or haematoma were commonly seen adverse events related to acupuncture treatment and recommended a consent form prior to treatment (Witt, Pach et al., 2009).
In addition, CHM or acupuncture treatment can only be delivered by experienced practitioners and attending an acupuncture clinic to receive acupuncture treatment is considered more time-consuming compared with taking medication.

Therefore, although positive findings from some studies suggest that CHM and acupuncture may be effective for AR, for the AR patients who are seeking CAM therapies, a non-invasive and safer form of CAM should be considered if it is also effective.

Ear-acupressure is a subtype of acupuncture that may be an effective and safe method. Firstly, ear-acupressure applies stimulation on acupoints by pressure instead of needle penetration, so that the adverse events caused by needling can be avoided. Secondly, ear-acupressure is semi-self-administered by patients, thus the intensity of pressure can be controlled based on patients’ own feeling. More details on ear-acupressure will be introduced in Chapter 4.
Ear-acupuncture and ear-acupressure (also called auricular therapy) is a subtype of acupuncture. Ear-acupressure is a non-invasive technique of auricular therapy. This chapter briefly introduces the background of auricular therapy and furthermore the specific ear-acupressure techniques. Two systematic reviews on ear-acupuncture/ear-acupressure that were conducted prior to the clinical trial are presented in this chapter.

4.1 Background

Auricular therapy is a form of CAM treatment based on the theory that the ear is a microsystem in which the entire body is represented. By stimulating certain points on the ear, therapeutic effects can be achieved.

4.1.1 The development of auricular therapy

Auricular therapy has a long history of development and its origin can be dated back to ancient China. According to the theory of the meridian system in Chinese medicine, all the meridians are connected to the ear directly or indirectly. In traditional acupuncture, the points around the ear were used as part of the major meridians or channels. The Eber's papyrus of 1550 BC (now in the British Museum) also describes a system of channels and vessels in the body which approximates more closely the Chinese system of channels than any known system of blood vessels, lymph vessels or nerves. The Egyptologist Alexandre Varille has documented that women in ancient Egypt who did not want any more children, had their external ear pricked with a needle or cauterized with heat. Hippocrates, the father of Greek
medicine, reported that doctors made small openings in the veins situated behind the ear to facilitate ejaculation and reduce impotency problems (Gori & Firenzuoli, 2007).

The current system of auricular acupuncture was originally presented by Nogier in 1956. Nogier is acknowledged as the “Father of Auricular Acupuncture”. He firstly observed patients in his practice who had received cauterisations on the ear’s antihelix for the treatment of sciatica. Nogier found that this was not only an occasional case, there were also some other practitioners delivering this treatment even though they were unaware how or why the procedure worked. By further investigation of this phenomenon, Nogier developed a mapping of “inverted foetus” and located 30 different points with an anatomical correspondence with the whole body. This technique was introduced to China and Japan in 1950s. Based on Nogier’s findings, the mapping of auricular acupoints was developed based more on functional considerations rather than from Nogier’s anatomical viewpoint. Detailed maps of the ear acupuncture points and zones were produced and incorporated into contemporary acupuncture texts.

The first time an official international organisation studied the subject of auricular acupuncture was in 1990, when the World Health Organisation (WHO) held a meeting of “the Standardization of the nomenclature of the auricular acupuncture points” (Frank & Soliman, 2006).

Today, auricular acupuncture is taught in the majority of Western countries. In France, teaching takes place in seven medicine faculties. There is a University diploma of auriculotherapy with the Paris faculty of Bobigny. In other European countries, this technique is also very popular, especially in Germany, Scandinavia, Spain and Italy
(Frank & Soliman, 2006). In Asian countries such as China, Japan, and Korea, this simple treatment is also widely applied due to its convenience and clinical effectiveness (Frank & Soliman, 2006).

4.1.2 Mechanism of auricular therapy

Auricular therapy considers the external ear as a microsystem of the whole body. Specific zones on the external ear represent certain areas of the body. Stimulating specific ear acupoints can produce therapeutic effects in the body for a large variety of conditions (Frank & Soliman, 2006).

However, the exact mechanism of auricular therapy remains unknown. One explanation of how auricular therapy may work (although not proven) is that the stimulation of certain nerves on the ear may send messages to the brain that will in turn generate a “response” to the part of the body to be treated. It may also stimulate a general relaxation of the body (Frank & Soliman, 2006).

Nowadays, there are two auricular therapy systems existing: the European system and Chinese system. In 1950’s, Nogier developed a three dimensional acupuncture microsystem. This system stresses that the organs are projected onto the ear as specific points within their respective zones. The practitioner should search for the active points within the organ’s zone for treatment (Frank & Soliman, 2006). The discovery of this system spread to China and led to intensive research by the Chinese medical authorities in late 1950s. A study initiated by the Nanjing Army Ear Acupuncture Research Team assessed over 2000 clinical patients and recorded the ear points that corresponded to the specific disease (Frank & Soliman, 2006). The Chinese ear-acupuncture system subsequently is focused on points’ functions and
the symptoms treated to build the charts, consequently some of the organs or structures differ from Nogier’s three phases chart (Frank & Soliman, 2006).

**4.1.3 Application of auricular therapy**

Auricular therapy can be applied through needling, using specifically designed machines or acupressure.

**4.1.3.1 Needling**

Similar to body acupuncture, needling should be applied to the ear points only after a complete sterilisation of the skin. Only needles with short length (13mm) or the press needles specifically designed for ear points can be used in ear-acupuncture. The insertion of needles should be no more than 2mm. Needles can be retained for 10-30 minutes (Frank & Soliman, 2006).

**4.1.3.2 Auricular electroacupuncture stimulation (AES)**

Once needles are inserted into certain points, electronic stimulation can be applied using specifically designed auricular electroacupuncture stimulation equipment. It is necessary to select two needles and connect these to the equipment with wires to obtain the electronic stimulation as the electricity flows from a positive to a negative pole. Both low frequencies of 2 Hz to 10 Hz or a high frequency of 100 Hz can be chosen. In theory, the low frequency stimulation will affect enkephalins, endorphins and visceral and somatic disorders, while high frequency stimulation will affect dynorphins and neurological dysfunction (Frank & Soliman, 2006).
4.1.3.3 Acupressure

Acupressure involves using the fingers, a round tip probe, magnetic or stainless steel pellets, or seeds to gently press and massage the points on the external ear to achieve therapeutic effects. The most commonly used ear-acupressure technique is attaching pellets or seeds to certain ear points using adhesive dressing to produce mild, long-term stimulation (Frank & Soliman, 2006).

In addition, other technique such as laser stimulation on ear points, or points’ prick blood-letting technique also has been adapted in auricular therapy (Frank & Soliman, 2006).

The auricular therapy (including ear-acupuncture and ear-acupressure) has been popularly used for both acute and chronic pain or anxiety related disorders (Barker et al., 2006; Berman, Lundberg, Krook, & Gyllenhammar, 2004; Karst et al., 2007). Some other common conditions treated by ear-acupuncture/ear-acupressure are weight loss (Li, Wang, Gu & Wang, 2004), drug dependence (Avants, Margolin, Holford, & Kosten, 2000), smoking or alcohol dependence (Sapir-Weise, Berglund, Frank, & Kristenson, 1999), insomnia (Suen, Wong, Leung, & Ip, 2003), menstrual or menopausal syndromes (Zhu & Zhang, 1996; S. M. Wang et al., 2009) and psychological disorders such as depression (MacPherson & Schroer, 2007).

4.1.4 Ear-acupressure for AR

Ear-acupressure method with attaching seeds or pellets has been clinically used for AR. As AR is defined as an allergic condition, points related to allergy should be selected. In addition, points related to nose may help with nasal symptoms, while those related to eyes may relieve eye symptoms.
In clinical research, there have been RCTs suggested that ear-acupressure was an effective and safe treatment for AR (Gao, Zhang, Zhu, & Zhang, 2008; Huo, 2003; Kong, Ren, & Lu, 2006; Qi & Wang, 2008; Rao & Han, 2006; Wang, 2004; Ye, Luo, & Xia, 2008). However, there was not any systematic review in this area. Therefore, a systematic review on ear-acupuncture/ear-acupressure for AR RCTs was conducted to assess the current evidence of ear-acupuncture/ear-acupressure’s effectiveness and safety for the management of AR, and also to specify the methodology of our clinical trial design. Furthermore, in order to determine the sham control method, another systematic review was conducted to investigate the sham design used in the previous ear-acupuncture/ear-acupressure RCTs.

4.2 Ear-acupuncture and ear-acupressure for AR: a systematic review

Although some clinical studies have found that ear-acupuncture or ear-acupressure is effective and safe for the management of AR (Gao, Zhang, Zhu, & Zhang, 2008; Qi & Wang, 2008; Rao & Han, 2006; Ye, Luo, & Xia, 2008), there lacks a systematic review to evaluate the current state of the evidence.

Therefore, a systematic review was conducted in 2008 before the commencement of the pilot study. An earlier version of the systematic review based on the literature search in 2008 has been published (Zhang et al., 2010). This systematic review was updated in January 2011. This chapter introduces the methodology and results of the systematic review with the recently updated information.
4.2.1 Objectives of the review

The main objective of this review was to assess the effectiveness and safety of ear-acupuncture or ear-acupressure for the treatment of AR. Secondary objectives included: determining which ear-acupuncture points were used in existing trials; gathering data on study design and procedure and effect size to inform the proposed randomised controlled trial.

4.2.2 Methods

The literature search was conducted in April 2008 and updated in January 2011, following the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (Higgins & Green, 2006).

4.2.2.1 Search strategy

A total of 21 electronic databases were searched from their respective inceptions to January 2011, 19 of them were English databases and two were Chinese databases. They are listed in Table 10.
### Table 10: Databases searched for the systematic review on ear-acupuncture and ear-acupressure for AR

<table>
<thead>
<tr>
<th>English databases</th>
<th>Chinese databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cochrane Central Register of Controlled Trials</td>
<td>• VIP Information (<a href="http://www.cqvip.com">www.cqvip.com</a>)</td>
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<tr>
<td>• PubMed</td>
<td>• China National Knowledge Infrastructure (<a href="http://www.cnki.net">www.cnki.net</a>)</td>
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<tr>
<td>• EMBASE</td>
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<td>• CINAHL</td>
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<td>• Informit</td>
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<td>• Science Direct</td>
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<tr>
<td>• LILACS (Latin American and Caribbean Health Sciences)</td>
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<td>• ProQuest</td>
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<td>• AMED</td>
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<td>• Blackwell Synergy</td>
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<td>• PSYCINFO</td>
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<td>• PANTELEIMON</td>
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<td>• AcuBriefs</td>
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<td>• Koreamed</td>
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<td>• INDMED</td>
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<td>• Ingenta</td>
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<tr>
<td>• mRCT</td>
<td></td>
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<tr>
<td>• ISI web of knowledge</td>
<td></td>
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<td>• ERIC</td>
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</tr>
</tbody>
</table>

Key words used throughout the search process included the combination of ear, auricular, acupuncture, acupressure, acupoint, allergic, allergy, rhinitis, hayfever, randomised clinical trial and their synonyms. The strategy used for searching Pubmed is provided in Table 11 as an example. Similar search strategies were applied to other databases.
Table 11: Search strategy for the systematic review on ear-acupuncture and ear-acupressure for AR used for Pubmed

<table>
<thead>
<tr>
<th>#</th>
<th>Search Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>ear or auricular</td>
</tr>
<tr>
<td>#2</td>
<td>acupuncture or acupressure or acupoint</td>
</tr>
<tr>
<td>#3</td>
<td>#1 and #2</td>
</tr>
<tr>
<td>#4</td>
<td>allergic or allergy</td>
</tr>
<tr>
<td>#5</td>
<td>rhinitis*</td>
</tr>
<tr>
<td>#6</td>
<td>#4 and #5</td>
</tr>
<tr>
<td>#7</td>
<td>hay fever or hayfever</td>
</tr>
<tr>
<td>#8</td>
<td>#6 or #7</td>
</tr>
<tr>
<td>#9</td>
<td>clinical trial or clinical trials</td>
</tr>
<tr>
<td>#10</td>
<td>clinical study</td>
</tr>
<tr>
<td>#11</td>
<td>#9 or #10</td>
</tr>
<tr>
<td>#12</td>
<td>random*</td>
</tr>
<tr>
<td>#13</td>
<td>#11 and #12</td>
</tr>
<tr>
<td>#14</td>
<td>#3 and #8 and #13</td>
</tr>
</tbody>
</table>

4.2.2.2 Study selection

Upon the completion of the searches of the electronic databases, two independent reviewers initially screened all study titles and abstracts. Based on the selection criteria, if the study titles and abstracts did not provide adequate information, the full-text articles were then obtained for further screening. Any disagreement between two reviewers was resolved by a third party researcher. The selection criteria are:

Inclusion criteria:

- RCTs or quasi-RCTs;
- Patients with any type of AR and of any age or gender;
- Intervention: any type of ear-acupuncture or ear-acupressure;
- Control: sham/placebo, no intervention, acupuncture, CHM or conventional therapies;
- Co-intervention: co-intervention is allowed as long as all the arms of the trial use the same co-intervention;
- Outcome measures: any type of outcome measure.

Exclusion criteria:
- Animal experiments;
- Non-RCTs or non-quasi-RCTs;
- Non AR;
- Non ear-acupuncture or ear-acupressure studies;
- Co-intervention that is not in all the arms of a RCT.

For all the included studies, full texts were obtained for further evaluation.

4.2.2.3 Methodological quality assessment, data extraction and data analysis

This review was conducted in 2008 following the Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (Higgins & Green, 2006). Jadad scale was employed for the methodological quality assessment rather than the risk of bias tool which was introduced by later version of the Cochrane Handbook (Cochrane Handbook for Systematic Reviews of Interventions 5.1.0) (Higgins & Green, 2011). For all the included studies, two reviewers independently assessed the methodological quality of using the 6 point (0-5) Jadad scale (Jadad et al., 1996). Details of this scale have been provided in section 3.4.

The two reviewers also extracted data from the included studies independently as follows: study setting, sample sizes, the treatment and control interventions,
outcomes, and adverse events. Any discrepancy between the two reviewers was discussed with the third party to reach agreement. The heterogeneity of the studies was interpreted through the characteristics of interventions.

Effect size analysis was performed to explore the differences between interventional groups. Dichotomous data were expressed as risk ratio (RR) with 95% confidence interval (CI). Continuous data were not reported in all included RCTs.

4.2.3 Results

A total of 103 studies were identified following the search strategy. By screening the titles and abstracts, 36 of them were excluded due to not meeting the inclusion criteria, 67 full-text manuscripts were retrieved for detailed evaluation. After screening the full articles, 60 were excluded and seven studies were included in this review (Gao, Zhang, Zhu, & Zhang, 2008; Huo, 2003; Kong, Ren, & Lu, 2006; Qi & Wang, 2008; Rao & Han, 2006; Wang, 2004; Ye, Luo, & Xia, 2008).

The details of study selection process are shown in Figure 9.
Figure 9: Flow chart of the study selection process (SR1)
4.2.3.1 Characteristics of included studies

All seven included studies were conducted in mainland China and published in Chinese language. The study sample sizes ranged from 66 to 400. A total of 1,004 participants with AR, aged from 5 to 66 years, were randomised and 996 participants were analysed in these seven original studies. Only one study reported withdrawals (Rao & Han, 2006), eight participants discontinued during the treatment period and they were not included in the data analysis.

Of the seven included studies, four studies (Gao, Zhang, Zhu, & Zhang, 2008; Qi & Wang, 2008; Rao & Han, 2006; Ye, Luo, & Xia, 2008) provided diagnostic criteria as the Chinese version “AR diagnostic and effects criteria”. However, none of the studies stated detailed inclusion or exclusion criteria. The number of treatment sessions and their total treatment duration varied in these studies, ranging from five to 30 times and 18 to 84 days respectively, except for one study that did not provide details (Gao, Zhang, Zhu, & Zhang, 2008). Two studies (Rao & Han, 2006; Wang, 2004; Ye, Luo, & Xia, 2008) employed a 6-month follow-up period and one study had a one-year follow-up period (Gao, Zhang, Zhu, & Zhang, 2008), the other studies (Huo, 2003; Kong, Ren, & Lu, 2006; Qi & Wang, 2008; Wang, 2004) did not have a follow-up period. In terms of the intervention, all the seven included studies involved ear-acupressure as the active treatment intervention. One study (Ye, Luo, & Xia, 2008) used magnetic pellets to press the ear points; three studies (Qi & Wang, 2008; Wang, 2004; Ye, Luo, & Xia, 2008) used Semen Vaccariae (cow soapwort seed or Wang Bu Liu Xing); one study (Gao, Zhang, Zhu, & Zhang, 2008) used “magnetic pellets or Semen Vaccariae”; whilst two other studies (Huo, 2003; Kong, Ren, & Lu, 2006) did not provide details of the instruments used for ear-acupressure. There were a total of 14 different ear points used in these seven studies, among them,
Internal nose (TG₄), External nose (TG₁₂₀₁) were used in all studies, Lung (CO₁₄) and Spleen (CO₁₃) were used in six studies, Throat, Shenmen (TF₄) and Adrenal Gland (TG₂P) were selected by four studies. Details are summarised in Table 12.

Table 12: Summary of ear points used in the included RCTs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal nose (TG₄)</td>
<td>7</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>External nose (TG₁₂₀₁)</td>
<td>7</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lung (CO₁₄)</td>
<td>6</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Spleen (CO₁₃)</td>
<td>6</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Throat (TG₃)</td>
<td>4</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Shenmen (TF₄)</td>
<td>4</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Adrenal Gland (TG₂P)</td>
<td>4</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Liver (CO₁₂)</td>
<td>3</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Kidney (CO₁₀)</td>
<td>3</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Eye (LO₅)</td>
<td>3</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Jiaogan (AH₆₆a)</td>
<td>2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Wind stream (SF₁₂₀₁)</td>
<td>2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Neifenmi (CO₁₈)</td>
<td>1</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Heart (CO₁₅)</td>
<td>1</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Concerning the control methods used for the control group in the seven studies, two studies (Kong, Ren, & Lu, 2006; Wang, 2004) compared ear-acupressure with CHM tablets; two studies (Huo, 2003; Qi & Wang, 2008) compared ear-acupressure with body acupuncture; one study (Ye, Luo, & Xia, 2008) compared ear-acupressure plus body acupuncture with body acupuncture alone; one study (Gao, Zhang, Zhu, & Zhang, 2008) compared ear-acupressure with an anti-histamine medication (Loratadine); while another study (Rao & Han, 2006) was a three-armed trial that
compared ear-acupressure with body acupuncture or with an anti-histamine medication (Cetirizine).

With regard to outcome measures, five out of the seven studies only used “Total effective rate” as their outcome measure (Gao, Zhang, Zhu, & Zhang, 2008; Huo, 2003; Kong, Ren, & Lu, 2006; Wang, 2004; Ye, Luo, & Xia, 2008). The “Total effective rate” was calculated as:

\[
\text{the number of cases that experienced AR symptom improvement after treatment} \times 100\% \over \text{the total number of cases in the group}
\]

When calculating this “Total effective rate”, all patients who experienced any symptom improvement, from minor improvement to significant improvement, were considered to be effective cases.

Three studies employed a symptom severity scoring system (Gao, Zhang, Zhu, & Zhang, 2008; Qi & Wang, 2008; Rao & Han, 2006). Four symptoms were scored using a three point scale (1, 2 and 3) including sneezing, runny nose, blocked nose and itchy nose. In these studies, this scoring method was used for “Total effective rate” data analysis. All the cases with more than 20% of symptom severity score reduction after treatment were considered effective cases. In addition to this scoring method, the study (Rao & Han, 2006) also measured total serum IgE, IL-4, and IFN-\(\gamma\).

The detailed characteristics of the included studies are summarised in Table 13.
Table 13: Characteristics and methodological quality assessment of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Diagnostic criteria</th>
<th>Sample size</th>
<th>Intervention</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huo, 2003</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Treatment (n, age): 30 (22-65): 17 in Lung and Spleen Qi deficiency subgroup; 13 in Phlegm-heat with blood stasis subgroup; Control (n, age): 36 (20-62): 22 in Lung and Spleen Qi deficiency subgroup; 16 in Phlegm-heat with blood stasis subgroup</td>
<td>Ear-acupressure: Neibi, Waibi, Eye, Shenshangxian, Liver, Spleen, Lung; Prick blood at Fengxi, Erjian; twice a week, 5 times, 2.5 weeks in total. Body acupuncture: twice a week, 5 times, 2.5 weeks in total.</td>
<td>1</td>
</tr>
<tr>
<td>Wang, 2004</td>
<td>Hospital outpatients</td>
<td>Unclear</td>
<td>Treatment (n, age): 300 (5-59)</td>
<td>Ear-acupressure (Wangbuliuxing seeds): Shenmen, Liver, Kidney, Spleen, Lung, Heart, Eye, Nose; once every 3 days, 10 times, 30 days in total. Bi Yan Kang (Rhinitis Tablets): 4 tablets, tid, 30 days in total.</td>
<td>1</td>
</tr>
<tr>
<td>Kong, 2006</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Treatment (n, age): 54 (14-62)</td>
<td>Ear-acupressure (seeds): Neibi, Waibi, Fei, Shenshangxian (main ear points); once every 4 days, 21 times, 84 days in total. Fang Zhi Bi Yan Pian (Fang Feng and Bai Zhi Rhinitis Tablets): 5 tablets, tid; and Fu Ma Liquid: 2 nasal drops, tid; 21 days in total.</td>
<td>1</td>
</tr>
<tr>
<td>Rao, 2006</td>
<td>Hospital outpatients</td>
<td>AR diagnostic and effects criteria</td>
<td>Treatment (n, age): 50 (16-65), 4 dropouts</td>
<td>T1: Body acupuncture; once a day for 28 days in total. T2: Ear-acupressure (Wangbuliuxing seeds): Fei, Pi, Shen, Neibi, Waibi, Fengxi, Neifenmi, Shenshangxian; twice a week for 4 weeks, 28 days in total. Cetirizine: 10mg, Qd, 28 days in total.</td>
<td>2</td>
</tr>
<tr>
<td>Author</td>
<td>Type</td>
<td>AR diagnostic and effects criteria</td>
<td>Number (Range)</td>
<td>Treatment</td>
<td>Duration</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>-----------------------------------</td>
<td>----------------</td>
<td>---------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Gao, 2008</td>
<td>Hospital outpatients</td>
<td>Ear acupressure (Wangbuliuxing seeds or magnetic pellets): Lung, Nose, Jiaogan, Fengxi, Throat, Shenmen, Kidney; once in every 3-4 days, the total duration is unclear.</td>
<td>33 (6.5-57)</td>
<td>33 (8-58)</td>
<td>Loratadine: 10mg, Qd, 28 days in total.</td>
</tr>
<tr>
<td>Qi, 2008</td>
<td>Unclear</td>
<td>Ear acupressure (Wangbuliuxing seeds): Neibi, Waibi, Jiaogan, Shenshangxian; once every 2 days, 10 times; 20 days in total.</td>
<td>50 (16-66)</td>
<td>50 (17-67)</td>
<td>Body acupuncture: once daily, 20 times; 20 days in total.</td>
</tr>
<tr>
<td>Ye, 2008</td>
<td>Hospital outpatients</td>
<td>Ear-acupressure (magnetic pellets): Shenmen, Gan, Shen, Pi, Fei, Mu, Bi, Yan; once every 2 days, 30 times; 60 days in total.</td>
<td>40 (10-61)</td>
<td>40 (10-61)</td>
<td>Body acupuncture: once every 2 days, 30 times; 60 days in total.</td>
</tr>
</tbody>
</table>

Legend: T: Treatment; C: Control. Tid: three times a day; Qd: once a day.

Texts in italic indicate that they are terms used in traditional Chinese medicine, acupuncture point names or herbal medicine names.
Table 14: Outcome measures and results of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Effect size RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Treatment group</strong></td>
<td><strong>Control group</strong></td>
</tr>
<tr>
<td>Huo, 2003</td>
<td>Total effective rate</td>
<td><em>Lung and Spleen Qi deficiency subgroup</em> (subgroup 1)</td>
<td>90.9% 64.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Phlegm-heat with blood stasis subgroup</em> (subgroup 2)</td>
<td>64.3% 100%</td>
</tr>
<tr>
<td>Wang, 2004</td>
<td>Total effective rate</td>
<td></td>
<td>99% 40%</td>
</tr>
<tr>
<td>Kong, 2006</td>
<td>Total effective rate</td>
<td></td>
<td>92.6% 70.4%</td>
</tr>
<tr>
<td>Rao, 2006</td>
<td>Total effective rate</td>
<td><strong>Treatment group 1</strong> (T1)</td>
<td><strong>Treatment group 2</strong> (T2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short term (after treatment)</td>
<td>95.75% 93.88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long term (6 months follow-up)</td>
<td>69.05% 58.97%</td>
</tr>
<tr>
<td>Gao, 2008</td>
<td>Total effective rate</td>
<td>Short term (after treatment)</td>
<td>87.88% 90.91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long term (12 months follow-up)</td>
<td>45.45% 33.33%</td>
</tr>
<tr>
<td>Qi, 2008</td>
<td>Total effective rate</td>
<td></td>
<td>96% 100%</td>
</tr>
<tr>
<td>Ye, 2008</td>
<td>Total effective rate</td>
<td></td>
<td>97.5% 80.0%</td>
</tr>
</tbody>
</table>

Legends: RR: Risk Ratio; CI: Confidence Interval; T: Treatment; C: Control.

Note: Texts in *italic* indicate that they are terms in traditional Chinese medicine.
4.2.3.2 Methodological quality of included studies

Randomisation was claimed in all the studies. One study provided the details of using the odd/even alternative allocation method for randomisation (Huo, 2003); another study used the sequence of clinic attendance for randomisation (Gao, Zhang, Zhu, & Zhang, 2008) and the rest did not give details of randomisation methods used. None of the seven studies provided information on blinding. In addition, none of them applied the sham/placebo control method or intention-to-treat analysis. Only one study (Rao & Han, 2006) reported dropouts/withdrawals. Therefore, the Jadad scores of the included studies ranged from 0 to 2 (only Rao & Han’s) study was scored with 2). All these studies were considered to be of low quality. The detailed Jadad scores of the included studies are provided in Table 13 (page 115).

4.2.3.3 Clinical effectiveness

Two studies (Kong, Ren, & Lu, 2006; Wang, 2004) reported that the ear-acupressure produced a significantly higher percentage of effectiveness comparing with CHM (RR, 1.32; 95%CI: 1.09, 1.59 and RR, 2.48; 95%CI: 1.95, 3.15). Rao and Han (2006) found that ear-acupressure was not better than body acupuncture (RR, 0.98; 95%CI: 0.89, 1.08) or anti-histamine (cetirizine) (RR, 0.96; 95%CI: 0.88, 1.04) in the short-term (four weeks) based on the percentage of cases with symptom severity score reduction. However, this study found that ear-acupressure had a significantly better long-term (six months) effect than the anti-histamine medication (RR, 3.02; 95%CI: 1.54, 5.93). Rao and Han (2006) also reported that both acupuncture and ear-acupressure had similar short-term effects (no data available for long-term follow-up) to anti-histamine in reducing the total serum IgE ($p$<0.01) and IL-4 ($p$<0.05). Similarly, Gao et al. (2008) reported that ear-acupressure was not better than body acupuncture (RR, 0.97; 95%CI: 0.82, 1.14) in the short-term but more effective in the
long-term (RR, 1.36; 95%CI: 0.74, 2.51). Qi and Wang (2008) found that ear-acupressure was less effective compared with anti-histamine medication (RR, 0.96; 95%CI: 0.90, 1.03).

Another study concluded that when ear-acupressure was combined with body acupuncture, the combined effect was superior to that of body acupuncture alone (RR, 1.22; 95%CI: 1.04, 1.43) (Ye, Luo, & Xia, 2008).

Huo's study (Huo, 2003) divided patients into subgroups according to Chinese medicine principles as follows: Lung and Spleen Qi deficiency and Phlegm-heat with blood stasis syndrome. It concluded that ear-acupressure had better effects than body acupuncture treatment for participants with Lung and Spleen Qi deficiency syndromes. However, there was no difference in the participants with phlegm-heat and blood stasis when compared with body acupuncture (RR, 0.66; 95%CI: 0.44, 0.98). When all participants are combined, the two treatments showed similar clinical outcomes (RR, 1.01; 95%CI: 0.79, 1.28).

The outcome measures and results are summarised in Table 14 (page 117).

4.2.3.4 Adverse events reported in the included studies

Three studies (Kong, Ren, & Lu, 2006; Rao & Han, 2006; Wang, 2004) indicated that there were no adverse events observed. The other four studies (Gao, Zhang, Zhu, & Zhang, 2008; Huo, 2003; Qi & Wang, 2008; Ye, Luo, & Xia, 2008) did not provide information about adverse events.
4.2.4 Discussion and conclusion

This recently updated systematic review shows that only a small number RCTs of ear-acupressure for AR are available and all of these studies were conducted in China. All the included studies used non-invasive (no skin penetration) mechanical stimulation methods on the ear points such as seeds or magnetic pellets. There were no studies of ear acupuncture. Commonly used ear points involved in the ear-acupressure treatments were: Internal nose (TG₄), External nose (TG₁₂), Lung (CO₁₄) and Spleen (CO₁₃), Throat, Shenmen (TF₄) and Adrenal Gland (TG₂P). With regard to the control interventions, two studies compared ear-acupressure with CHM, three studies compared ear-acupressure with body acupuncture, one study compared ear-acupressure with anti-histamine medication (Loratadine) and one study compared ear-acupressure with body acupuncture as well as anti-histamine medication (Cetirizine). Since sham/placebo control was not used in any of the studies, it was not possible for the participants to be blinded. Therefore, the results from these unblinded RCTs tend to be biased (Wood et al., 2008).

Overall, the included RCTs showed that ear-acupressure appears to have a higher percentage of effectiveness than that produced by CHM. When comparing with body acupuncture, three studies (Huo, 2003; Qi & Wang, 2008; Rao & Han, 2006) reported ear acupressure had similar effectiveness to body acupuncture whereas another study (Ye, Luo, & Xia, 2008) concluded that the effect of combining ear-acupressure with body acupuncture was better than using body acupuncture alone. On the other hand, when comparing ear-acupressure with anti-histamine medication, two studies (Gao, Zhang, Zhu, & Zhang, 2008) and (Rao & Han, 2006) showed a better long-term effect for ear-acupressure. However, due to the fact that all included studies
were assessed as low quality, Meta-analysis was not applied to avoid generating false results.

Three studies (Kong, Ren, & Lu, 2006, Rao & Han, 2006, Wang, 2004) reported there were no adverse events associated with ear-acupressure. This may be due to the fact that, unlike standard needle acupuncture for which minor adverse events are usually reported (Witt et al., 2009), no skin penetration was involved in these studies.

Consistent with a recent review on CAM for rhinitis and asthma (Passalacqua et al., 2006), the methodological quality of included studies is low. The results for the 6-point Jadad scale (0 to 5) assessments of these seven studies were between 0 and 2. None of them provided adequate information on appropriate methods used for randomisation or concealment of allocation. Neither blinding techniques nor sham/placebo ear-acupressure control was applied to any of the included studies. Although the studies demonstrated positive results for ear-acupressure when compare with CHM (for the short-term) or anti-histamine medications such as Cetirizine and Loratadine (for the long-term), firm conclusions cannot be drawn due to the inappropriate control method. Selection criteria of participants were not clearly described in any of the included studies. Three studies (Gao, Zhang, Zhu, & Zhang, 2008; Qi & Wang, 2008; Rao & Han, 2006) used a symptom scoring method to measure the severity of symptoms, other four studies only employed “Total effective rate” as the outcome measures without a detailed scoring system. Quality of life improvement or reduction of medication usage, which have been widely used in other RCTs of AR in the English literature (Brinkhaus et al., 2008; Xue, English, Zhang, Da Costa, & Li, 2002; Xue et al., 2007) were not employed as outcome measures in any of the included studies. In addition, only the Rao and Han (2006) study included
laboratory serum tests. Due to the significant methodological weaknesses, the summarised results from this review must be interpreted with caution.

In conclusion, the existing evidence indicated that ear-acupressure was well tolerated by patients with AR. Although ear-acupressure has shown some promising positive effects for symptomatic relief of AR, the findings should be carefully interpreted due to the lack of blinding, lack of a sham/placebo control and general low methodological quality of the included trials. To provide reliable evidence to guide clinical practice, a more rigorously designed RCT of ear-acupressure for AR is needed.

4.3 Sham control methods used in ear-acupressure RCTs: a systematic review

The systematic review discussed in section 4.2 showed that the previous RCTs of ear-acupuncture/ear-acupressure suffered from methodological flaws including lack of appropriate control methods.

In clinical research, RCTs are generally considered as the gold standard experiment to provide evidence for the efficacy of the intervention (Devereaux & Yusuf, 2003). In drug trials the control used is an inert placebo that is designed to be identical to the active intervention and thereby reduce the risk of unblinding the participants to their group allocation. However, if the intervention to be tested is a physical procedure, the design of the control methods becomes more complex.

“Sham” is the term used to refer to a faked operative intervention which is used in the same manner as a placebo to enable blinding and reduce bias. The methodological
difficulties in designing proper placebo/sham control interventions in experiments on physical interventions such as acupuncture or acupressure has been the topic of considerable discussion (White, Filshie, & Cummings, 2001).

A review of sham interventions used in RCTs of acupuncture (Dincer & Linde, 2003) has been completed. Forty-seven RCTs comparing real and sham acupuncture interventions for pain and a variety of other conditions were identified in this review. This review reported that the sham interventions of acupuncture methods could be categorised into five types:

- Superficial needling of “true” acupuncture points (superficial needling of the acupoints for the treated condition)
- Irrelevant acupuncture points (normal needling of acupoints that are not used for the treated condition)
- Non-acupuncture points (needling non-acupoints)
- Placebo needles (devices that mimic acupuncture without skin penetration)
- Pseudo-interventions (interventions that are not “true” acupuncture e.g. use of switched-off laser acupuncture devices)

Among these five types of sham intervention, the “non-acupuncture points” method was the most commonly used. The findings from this review have assisted researchers in designing their acupuncture RCTs (Thomas et al., 2006; Xue et al., 2007).

Similar to the RCTs on acupuncture or other physical interventions, sham/placebo control groups have also been used in ear-acupuncture/ear-acupressure studies. Unlike body acupuncture, it is difficult to locate non-acupuncture points on the ear due to the small size of the ear and the large number of identified acupoints on the
ear. In the design of an ear-acupuncture/ear-acupressure study, choosing a suitable control method to ensure the participant blinding is important. To date, there is no published critical review on the control intervention methods used in ear-acupuncture/ear-acupressure trials.

Therefore, prior to designing the ear-acupressure for AR RCT, a systematic review was conducted in April 2008 and updated in January 2011 to investigate all types of sham/placebo ear-acupuncture/ear-acupressure methods by reviewing all published RCTs that have used sham/placebo ear-acupuncture/ear-acupressure as a control intervention. This section details the methods and results of the systematic review including the recently updated information.

4.3.1 Methods of the review

This review was conducted in 2008 following the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (Higgins & Green, 2006).

4.3.1.1 Search strategy

Consistently with the systematic review 1, a total of 19 electronic English databases and two Chinese databases were searched from their respective inceptions to the end of January 2011 (details refer to Table 10, page 107). Key words used for the search included the combination of ear, auricular, acupuncture, acupressure, randomised controlled trial and their synonyms.

4.3.1.2 Study selection

The study selection procedure was consistent with systematic review 1 (section 4.2.2.2). The study selection criteria were:
Inclusion criteria:

- RCTs and quasi-RCTs;
- Patients with any type of clinical condition, any age or gender;
- Intervention: any type of ear-acupuncture or ear-acupressure (such as needles inserting into ear points, electrical stimulation on the ear points, laser stimulation on the ear points, seeds, stainless steel pellets or magnetic pellets attached on ear points, or prick blood-letting technique on ear points);
- Control: any type of sham/placebo ear-acupuncture or ear-acupressure control, even if the term “sham/placebo” is not mentioned in the article; and
- Co-intervention is allowed as long as all the arms used the same co-intervention;
- Published in English or Chinese;
- Any type of outcome measures.

Exclusion criteria:

- Studies not for a clinical condition;
- Studies that are not a sham/placebo-controlled trial; and
- Studies that do not assess the efficacy of ear-acupuncture/ear-acupressure.

For all the included studies, full texts were obtained for further evaluation.

### 4.3.1.3. Classification of sham interventions

Consistent with the sham acupuncture review (Dincer & Linde, 2003), the sham interventions used in the included studies were categorised according to the following classification:

- Type I: non-specific ear points for the condition treated;
- Type II: non-ear points;
- Type III: placebo needles or adhesive patches; and
- Type IV: pseudo-interventions (eg. switched off laser acupuncture devices, electro acupuncture devices with minimum emission, Vaccariae seeds without pressing).

4.3.1.4 Data analysis

The types of interventions were summated. The differences between real and sham interventions were then examined, including the number and location of ear points, achievement of De Qi sensation (the feelings occur after an acupuncture needle has been properly placed in the body, such as numbness, heaviness, and other feelings, which is usually considered as an important component of acupuncture treatment), number and duration of treatment sessions. Studies were clustered according to the main outcome measures used for the type of condition, such as pain intensity for pain, State-Trait Anxiety Inventory (STAI) for anxiety and smoking cessation rate for smoking cessation. The results for the main outcome measures were summarised as: T>C (real treatment group was significantly superior to sham control group), ND (no differences between real and sham groups) and T<C (real treatment group was significantly inferior to sham control group). For the RCTs treating the same clinical condition, data syntheses were conducted when data was available for the same outcome measure in two or more RCTs using the same sham control intervention. For trials with a comparable baseline, mean and standard deviation, data were entered into Cochrane software Review Manager (RevMan) 5 for meta-analysis. Continuous data were presented as mean difference (MD) (if the same scales were used for the same outcome measure) or standard mean difference (SMD) (if different scales for the same outcome measure were used), and RR was used for dichotomous data, both approaches used a 95% CI.
4.3.2 Results

A total of 62 articles were identified and 37 of them were sham-controlled RCTs and were included in the current review. The study selection process is shown in Figure 10.
Figure 10: Flow chart of the study selection process (SR2)

4.3.2.1 Description of included studies

Clinical conditions treated in the included studies consist of:
• Pain: 11 studies (Alimi et al., 2003; Mazzetto, Carrasco, Bidinelo, de Andrade Pizzo, & Mazzetto, 2007; Michalek-Sauberer et al., 2007; Sator-Katzenschlager et al., 2004; Sator-Katzenschlager et al., 2003; Sator-Katzenschlager et al., 2006; Simmons & Oleson, 1993; Usichenko et al., 2005; Usichenko et al., 2007; Wang, Hsu, Chien, Kao, & Liu, 2009; Wang et al., 2009)

• Anxiety: six studies (Karst et al., 2007; Kober et al., 2003; Mora et al., 2007; Wang & Kain, 2001; Wang, Maranets, Weinberg, Caldwell-Andrews, & Kain, 2004, Wang, Peloquin, & Kain, 2001);

• Drug dependence: nine studies (Avants, Margolin, Holford, & Kosten, 2000; Berman, Lundberg, Krock, & Gyllenhammar, 2004; Bullock, Kiresuk, Pheley, Culliton, & Lenz, 1999; Bullock et al., 2002; Killeen et al., 2002; Lipton, Brewington, & Smith, 1994; Margolin, Avants, & Holford, 2002; Tian & Krishnan, 2006; Washburn et al., 1993);

• Smoking cessation: five studies (Cai, Changxin, Ung, Lei, & Kean, 2000; Otto, Quinn, & Sung, 1998; Waite & Clough, 1998; White, Resch, & Ernst, 1998; Wu, Chen, Liu, Lin, & Hwang, 2007);

• Alcohol dependence: two studies (Sapir-Weise, Berglund, Frank, & Kristenson, 1999; Trumpler, Oez, Stahli, Brenner, & Juni, 2003);

• Insomnia: one study (Sjoling, Rolleri, & Englund, 2008);

• Body weight reduction: two studies (Hsu et al., 2009; Shen, Hsieh, Chang, & Lin, 2009);

• One study was for both anxiety and pain (Barker et al., 2006).

Among these 37 studies, five studies (Barker et al., 2006; Kober et al., 2003; Mora et al., 2007; Tian & Krishnan, 2006; Wang, Hsu, Chien, Kao, & Liu, 2009) employed
ear-acupressure as the intervention, while other studies used ear-acupuncture. Electro-acupuncture was involved in six studies (Michalek-Sauberer et al., 2007; Sator-Katzenschlager et al., 2004; Sator-Katzenschlager et al., 2003; Sator-Katzenschlager et al., 2006; Simmons & Oleson, 1993; White, Resch, & Ernst, 1998). One study (Trumpler, Oez, Stahli, Brenner, & Juni, 2003) selected laser stimulation as the intervention.

With respect to efficacy, 21 out of 37 trials showed the real ear-acupuncture/ear-acupressure groups had a significant superiority over the sham control groups (Alimi et al., 2003; Avants, Margolin, Holford, & Kosten, 2000; Barker et al., 2006; Kober et al., 2003; Mazzetto, Carrasco, Bidinelo, de Andrade Pizzo, & Mazzetto, 2007; Mora et al., 2007; Sator-Katzenschlager et al., 2004; Sator-Katzenschlager et al., 2003; Sator-Katzenschlager et al., 2006; Shen, Hsieh, Chang, & Lin, 2009; Simmons & Oleson, 1993; Tian & Krishnan, 2006; Usichenko et al., 2005; Usichenko et al., 2007; Waite & Clough, 1998; Wang & Kain, 2001; Wang, Maranets, Weinberg, Caldwell-Andrews, & Kain, 2004; Wang, Peloquin, & Kain, 2001; Wang, Hsu, Chien, Kao, & Liu, 2009; Wang et al., 2009; Washburn et al., 1993). The remaining 16 studies found that there were no significant differences between the real and sham groups (Berman, Lundberg, Krook, & Gyllenhammar, 2004; Bullock, Kiresuk, Pheley, Culliton, & Lenz, 1999; Bullock et al., 2002; Cai, Changxin, Ung, Lei, & Kean, 2000; Hsu et al., 2009; Karst et al., 2007; Killeen et al., 2002; Lipton, Brewington, & Smith, 1994; Margolin, Avants, & Holford, 2002; Michalek-Sauberer et al., 2007; Otto, Quinn, & Sung, 1998; Sapir-Weise, Berglund, Frank, & Kristenson, 1999; Sjoling, Rolleri, & Englund, 2008; Trumpler, Oez, Stahli, Brenner, & Juni, 2003; White, Resch, & Ernst, 1998; Wu, Chen, Liu, Lin, & Hwang, 2007). No studies found the sham group to be superior.
Except for four trials which did not report the data (Michalek-Sauberer et al., 2007; Otto, Quinn, & Sung, 1998; Sapir-Weise, Berglund, Frank, & Kristenson, 1999; Usichenko et al., 2007), the total number of treatment sessions ranged from one session to 40 sessions, and the frequency of treatment ranged from daily to weekly treatment. Thirteen studies (Barker et al., 2006; Karst et al., 2007; Killeen et al., 2002; Kober et al., 2003; Mora et al., 2007; Simmons & Oleson, 1993; Usichenko et al., 2005; Usichenko et al., 2007; Waite & Clough, 1998; Wang & Kain, 2001; Wang, Maranets, Weinberg, Caldwell-Andrews, & Kain, 2004; Wang, Peloquin, & Kain, 2001; Wang et al., 2009) only provided one real or sham treatment for the clinical condition. Seven studies treated either the real or sham ear points once a week (Shen, Hsieh, Chang, & Lin, 2009; Sator-Katzenschlager et al., 2004; Sator-Katzenschlager et al., 2003; Sator-Katzenschlager et al., 2006; Tian & Krishnan, 2006; Washburn et al., 1993; Wu, Chen, Liu, Lin, & Hwang, 2007); two trials treated twice a week (Hsu et al., 2009; Mazzetto, Carrasco, Bidinelo, de Andrade Pizzo, & Mazzetto, 2007); one study treated three times a week (Cai, Changxin, Ung, Lei, & Kean, 2000); and four trials used daily treatment (Bullock et al., 2002; Lipton, Brewington, & Smith, 1994; Margolin, Avants, & Holford, 2002; Trumpler, Oez, Stahli, Brenner, & Juni, 2003). The duration of treatment sessions varied greatly, lasting from 4 minutes to two weeks. Seven trials did not report the duration of treatment sessions (Barker et al., 2006; Bullock, Kiressuk, Pheley, Culliton, & Lenz, 1999; Kober et al., 2003; Mazzetto, Carrasco, Bidinelo, de Andrade Pizzo, & Mazzetto, 2007; Mora et al., 2007; Michalek-Sauberer et al., 2007; Usichenko et al., 2007).

None of studies indicated whether a De Qi sensation was achieved during the real ear-acupuncture/ear-acupressure treatment. Needle insertion depth on the ear points...
and manipulation on needles or seeds were not described in the majority trials. The characteristics of the included studies are summarised in Table 15.
<table>
<thead>
<tr>
<th>Sham control method</th>
<th>Condition</th>
<th>Condition subgroup</th>
<th>Author, Year</th>
<th>Analysed Sample Size (Groups T/C)</th>
<th>Ear-acupuncture or Ear-acupressure</th>
<th>No of Ear Points (T/C)</th>
<th>Unilateral or Bilateral Treatment</th>
<th>Treatment Sessions and total duration</th>
<th>Duration of Each Session</th>
<th>Result</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain and anxiety</td>
<td>Pain and Anxiety</td>
<td>Pain and anxiety</td>
<td>Barker, 2006</td>
<td>18/20 Ear-acupressure 3/1 Bilateral 1 session NS</td>
<td>T&gt;C, p=0.000 1, 0.018 5</td>
<td></td>
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<tr>
<td>Anxiety</td>
<td>Anxiety</td>
<td>Anxiety</td>
<td>Karst, 2007</td>
<td>19/19 Ear-acupuncture 3/2 NS 1 session 25 min</td>
<td>ND, p&gt;0.05 3</td>
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<td></td>
<td>Anxiety</td>
<td>Anxiety</td>
<td>Kober, 2003</td>
<td>17/19 Ear-acupressure 1/1 Bilateral 1 session NS</td>
<td>T&gt;C, p=0.002 4</td>
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<td></td>
<td>Anxiety</td>
<td>Anxiety</td>
<td>Mora, 2007</td>
<td>24/24 Ear-acupressure 1/1 Bilateral 1 session NS</td>
<td>T&gt;C, p=0.001 4</td>
<td></td>
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<tr>
<td></td>
<td>Anxiety</td>
<td>Anxiety</td>
<td>Wang, 2001a</td>
<td>22/15/18 (T1/T2/C) Ear-acupressure 1/1/1 Bilateral 1 session 48 hours</td>
<td>T2&gt;T1, C, p= 1</td>
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<td></td>
<td>Anxiety</td>
<td>Anxiety</td>
<td>Wang, 2001b</td>
<td>31/32/27 (T1/T2/C) Ear-acupressure 3/3/3 Unilateral 1 session 30 min</td>
<td>T2&gt;T1, C, p=0.001 1</td>
<td></td>
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<td></td>
<td>Anxiety</td>
<td>Anxiety</td>
<td>Wang, 2004</td>
<td>34/33 Ear-acupressure 3/3 Unilateral 1 session Various</td>
<td>T&gt;C, p=0.04 4</td>
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<tr>
<td>Pain</td>
<td>Pain</td>
<td>Pain</td>
<td>Simmons, 1993</td>
<td>10/10 Ear-acupressure 5/5 Unilateral 1 session 15 min</td>
<td>T&gt;C, p&lt;0.0001 3</td>
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<tr>
<td></td>
<td>Pain</td>
<td>Pain</td>
<td>Wang, 2009b</td>
<td>58/54 Ear-acupressure 3/3 Unilateral 1 session 1 week</td>
<td>T&gt;C, p=0.01 4</td>
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<tr>
<td>Substance abuse</td>
<td>Substance abuse</td>
<td>Substance abuse</td>
<td>Avants 2000</td>
<td>28/27 Ear-acupuncture 4/4 Bilateral 40 sessions within 8 weeks 40 min</td>
<td>T&gt;C, p=0.01 3</td>
<td></td>
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<tr>
<td>Drug dependence</td>
<td>Drug dependence</td>
<td>Drug dependence</td>
<td>Berman, 2004</td>
<td>32/44 Ear-acupuncture 5/5 Bilateral 14 session 40 min</td>
<td>ND, p&gt;0.05 2</td>
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<td></td>
<td>Drug dependence</td>
<td>Drug dependence</td>
<td>Bullock, 1999</td>
<td>236(NS) Ear-acupuncture 5/5 Bilateral 28 sessions within 8 weeks</td>
<td>ND, p=0.89 3</td>
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<td></td>
<td>Bullock, 2002</td>
<td>133/132</td>
<td>Ear-acupuncture</td>
<td>4/4</td>
<td>NS</td>
<td>18 sessions within 3 weeks</td>
<td>40 min</td>
<td>ND, $p&gt;0.05$</td>
<td>3</td>
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<tr>
<td>Killeen, 2002</td>
<td>15/15</td>
<td>Ear-acupuncture</td>
<td>5/5</td>
<td>NS</td>
<td>1 session</td>
<td>45 min</td>
<td>ND, $p=0.68$</td>
<td>1</td>
<td></td>
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<tr>
<td>Lipton, 1994</td>
<td>73/77</td>
<td>Ear-acupuncture</td>
<td>4/4</td>
<td>NS</td>
<td>$\geq 10$ sessions</td>
<td>45 min</td>
<td>ND, $p&gt;0.05$</td>
<td>3</td>
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<td>Margolin, 2002</td>
<td>222/203</td>
<td>Ear-acupuncture</td>
<td>4/3</td>
<td>Bilateral</td>
<td>40 sessions daily</td>
<td>40 min</td>
<td>ND, $p&gt;0.05$</td>
<td>5</td>
<td></td>
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<td>Washburn, 1993</td>
<td>55/45</td>
<td>Ear-acupuncture</td>
<td>4/4</td>
<td>Bilateral</td>
<td>5 sessions</td>
<td>20-45 min</td>
<td>T&gt;C, $p&lt;0.05$</td>
<td>2</td>
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<td>Smoking cessation</td>
<td>Otto, 1998</td>
<td>25/11</td>
<td>Ear-acupuncture</td>
<td>5/5</td>
<td>Bilateral</td>
<td>NS</td>
<td>30-40 min</td>
<td>ND, $p&gt;0.05$</td>
<td>4</td>
<td></td>
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<td></td>
<td>Wu, 2007</td>
<td>59/59</td>
<td>Ear-acupuncture</td>
<td>4/4</td>
<td>NS</td>
<td>8 sessions within 8 weeks</td>
<td>1 week</td>
<td>ND, $p&gt;0.05$</td>
<td>2</td>
<td></td>
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<tr>
<td>Alcohol dependence</td>
<td>Sapir-Weise, 1999</td>
<td>36/36</td>
<td>Ear-acupuncture</td>
<td>3/3</td>
<td>Bilateral</td>
<td>NS</td>
<td>45 min</td>
<td>ND, $p&gt;0.05$</td>
<td>5</td>
<td></td>
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<tr>
<td>Obesity</td>
<td>Shen, 2009</td>
<td>6/7</td>
<td>Ear-acupuncture</td>
<td>4/4</td>
<td>Unilateral</td>
<td>8 sessions within 8 weeks</td>
<td>1 week</td>
<td>T&gt;C, $p=0.03$</td>
<td>2</td>
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<td>Insomnia</td>
<td>Sjoling, 2008</td>
<td>14/14</td>
<td>Ear-acupuncture</td>
<td>5/5</td>
<td>Bilateral</td>
<td>15 sessions within 6 weeks</td>
<td>45 min</td>
<td>ND, $p&gt;0.05$</td>
<td>2</td>
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</tr>
</tbody>
</table>

<p>| Pain and Anxiety         | Alimi 2003   | 29/30   | Ear-acupuncture | NS | NS | 60 days | 43 min | T&gt;C, $p&lt;0.001$ | 3 |
|                         | Usichenko, 2005 | 31/30 | Ear-acupuncture | 4/4 | NS | 1 session | 3 days | T&gt;C, $p=0.004$ | 5 |
| Substance abuse (Alcohol, drug, smoking) | Usichenko, 2007 | 59/61 | Ear-acupuncture | 3/3 | NS | NS | NS | T&gt;C, $p=0.012$ | 5 |
| Smoking cessation        | Tian, 2006   | 5/4     | Ear-acupressure | 5/2 | Bilateral | 6 sessions within 6 weeks | 1 week | T&gt;C, $p=0.009$ | 3 |
|                         | Waite, 1998  | 40/38   | Ear-acupuncture | 1/1 | Bilateral | 1 session | 2 weeks | T&gt;C, $p&lt;0.05$ | 2 |</p>
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<thead>
<tr>
<th>Type III (placebo needles)</th>
<th>White, 1998</th>
<th>38/19</th>
<th>Ear-acupuncture</th>
<th>1/1</th>
<th>Bilateral</th>
<th>3 sessions within 7 days</th>
<th>20 min</th>
<th>ND, p&gt;0.05</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain and Anxiety</td>
<td>Wang, 2009a</td>
<td>36/35</td>
<td>Ear-acupressure</td>
<td>3/3</td>
<td>NS</td>
<td>NS</td>
<td>20 days</td>
<td>T&gt;C, p&lt;0.05</td>
<td>3</td>
</tr>
<tr>
<td>Obesity</td>
<td>Hsu, 2009</td>
<td>30/30</td>
<td>Ear-acupuncture</td>
<td>4/4</td>
<td>Unilateral</td>
<td>12 sessions within 6 weeks</td>
<td>3 days</td>
<td>ND, p&gt;0.05</td>
<td>3</td>
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<tr>
<td>Type IV (pseudo-intervention)</td>
<td>Mazzetto, 2007</td>
<td>24/24</td>
<td>Ear-acupuncture</td>
<td>1/1</td>
<td>Bilateral</td>
<td>8 sessions within 4 weeks</td>
<td>NS</td>
<td>T&gt;C, p&lt;0.05</td>
<td>3</td>
</tr>
<tr>
<td>Pain and Anxiety</td>
<td>Michalek-Sauberer, 2007</td>
<td>76/37</td>
<td>Ear-acupuncture</td>
<td>3/3</td>
<td>Unilateral</td>
<td>NS</td>
<td>NS</td>
<td>ND, p&gt;0.05</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sator-Katzenschlagrer, 2004</td>
<td>31/30</td>
<td>Ear-acupuncture</td>
<td>3/3</td>
<td>Unilateral</td>
<td>6 sessions within 6 weeks</td>
<td>48 hours</td>
<td>T&gt;C, p=0.021</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Sator-Katzenschlagrer, 2003</td>
<td>10/11</td>
<td>Ear-acupuncture</td>
<td>4/4</td>
<td>Unilateral</td>
<td>6 sessions within 6 weeks</td>
<td>48 hours</td>
<td>T&gt;C, p=N/A</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Sator-Katzenschlagrer, 2006</td>
<td>32/32</td>
<td>Ear-acupuncture</td>
<td>3/3</td>
<td>Unilateral</td>
<td>6 sessions within 6 weeks</td>
<td>48 hours</td>
<td>T&gt;C, p&lt;0.001</td>
<td>5</td>
</tr>
<tr>
<td>Substance abuse (Alcohol, drug, smoking)</td>
<td>Trumpler, 2003</td>
<td>17/16</td>
<td>Ear-acupuncture</td>
<td>NS</td>
<td>NS</td>
<td>&gt; 1 session</td>
<td>30-45 min</td>
<td>ND, p&gt;0.05</td>
<td>5</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Cai, 2000</td>
<td>128/140</td>
<td>Ear-acupuncture</td>
<td>4/4</td>
<td>Unilateral</td>
<td>12 sessions within 4 weeks</td>
<td>4 min</td>
<td>ND, p&gt;0.05</td>
<td>2</td>
</tr>
</tbody>
</table>

Legends: T: treatment group; T1: treatment group 1; T2: treatment group 2; C: control group; ND: no differences between real and sham groups; NS: not stated; Sham control method type: type I: Non-specific ear points; type II: Non ear point; type III: Placebo needles or adhesive patch, type IV: Pseudo-interventions.
4.3.2.2 Sham Interventions

Different sham control methods were used in these RCTs. Twenty-two trials selected non-specific ear points for the condition treated (Type I) (Avants, Margolin, Holford, & Kosten, 2000; Barker et al., 2006; Berman, Lundberg, Krook, & Gyllenhammar, 2004; Bullock, Kiresuk, Pheley, Culliton, & Lenz, 1999; Bullock et al., 2002; Karst et al., 2007; Killeen et al., 2002; Kober et al., 2003; Lipton, Brewington, & Smith, 1994; Margolin, Avants, & Holford, 2002; Mora et al., 2007; Otto, Quinn, & Sung, 1998; Sapir-Weise, Berglund, Frank, & Kristenson, 1999; Shen, Hsieh, Chang, & Lin, 2009; Simmons & Oleson, 1993; Sjoling, Rolleri, & Englund, 2008; Wang & Kain, 2001; Wang, Maranets, Weinberg, Caldwell-Andrews, & Kain, 2004; Wang, Peloquin, & Kain, 2001; Wang et al., 2009; Washburn et al., 1993; Wu, Chen, Liu, Lin, & Hwang, 2007). Among them, five studies selected points located on the helix (Avants, Margolin, Holford, & Kosten, 2000; Berman, Lundberg, Krook, & Gyllenhammar, 2004; Killeen et al., 2002; Margolin, Avants, & Holford, 2002; Sjoling, Rolleri, & Englund, 2008); three trials chose points at the tip of the concha (Kober et al., 2003; Mora et al., 2007; Wang & Kain, 2001); another five studies located non-specific ear points within 5mm from the specific points (Bullock, Kiresuk, Pheley, Culliton, & Lenz, 1999; Bullock et al., 2002; Lipton, Brewington, & Smith, 1994; Sapir-Weise, Berglund, Frank, & Kristenson, 1999; Washburn et al., 1993). The other nine trials did not provide the principles for selecting the non-specific ear points (Barker et al., 2006; Karst et al., 2007; Otto, Quinn, & Sung, 1998; Shen, Hsieh, Chang, & Lin, 2009; Simmons & Oleson, 1993; Wang, Maranets, Weinberg, Caldwell-Andrews, & Kain, 2004; Wang, Peloquin, & Kain, 2001; Wang et al., 2009; Wu, Chen, Liu, Lin, & Hwang, 2007).

Six trials used non-ear points as the sham control points (Type II) (Alimi et al., 2003;
Tian & Krishnan, 2006; Usichenko et al., 2005; Usichenko et al., 2007; Waite & Clough, 1998; White, Resch, & Ernst, 1998). Three chose non-ear points on the helix (Tian & Krishnan, 2006; Usichenko et al., 2005; Usichenko et al., 2007). Two trials used an electro acupuncture device to apply minimum stimulation on the non-ear points (Waite & Clough, 1998; White, Resch, & Ernst, 1998). One study chose points that did not show any electrical response when a probe was used (Alimi et al., 2003).

Two studies (Hsu et al., 2009; Wang, Hsu, Chien, Kao, & Liu, 2009) applied placebo needles (needles with blunt tips) or taped adhesive patches (without pellets or seeds) to the same ear points used in the real groups (Type III).

Six trials (Mazzetto, Carrasco, Bidinelo, de Andrade Pizzo, & Mazzetto, 2007; Michalek-Sauberer et al., 2007; Sator-Katzenschlager et al., 2003; Sator-Katzenschlager et al., 2006; Trumpler, Oez, Stahli, Brenner, & Juni, 2003; Cai, Changxin, Ung, Lei, & Kean, 2000) which employed laser acupuncture, electro acupuncture or magnetic pellets in the treatment intervention chose no or minimal stimulation on the same points in the sham control group (Type IV). The four types of control methods are summarised in Table 16.

Table 16: Types of sham interventions used in the 37 included studies

<table>
<thead>
<tr>
<th>Type of sham control</th>
<th>No. of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Non-specific ear points for the condition treated</td>
<td>22</td>
</tr>
<tr>
<td>II Non-ear points</td>
<td>6</td>
</tr>
<tr>
<td>III Placebo needles or adhesive patches</td>
<td>2</td>
</tr>
<tr>
<td>IV Pseudo-interventions (e.g. switched off laser acupuncture devices, electro acupuncture devices with minimum emission, Vaccariae seeds without pressing)</td>
<td>7</td>
</tr>
</tbody>
</table>
Three trials (Barker et al., 2006; Karst et al., 2007; Tian & Krishnan, 2006) used a lower number of ear points in the sham ear-acupuncture/ear-acupressure group than in the real treatment group. The rest of 34 trials applied the same number of ear points in both real and sham groups. All trials except one (Karst et al., 2007) applied the same real ear-acupuncture/ear-acupressure technique to both real and sham groups. Karst and his colleague’s study used placebo needles to treat non-specific ear points (Karst et al., 2007).
Meta-analysis

Data syntheses were attempted for 13 of the 37 RCTs as the remaining 24 trials did not provide adequate data for the major outcome measures. Due to heterogeneity and insufficient data reported for the included studies, data analysis could not be performed for alcohol dependence, body weight reduction, drug dependence and insomnia. Results from the data analyses for anxiety, pain and smoking cessation are reported as follows.

Anxiety

All the seven studies for anxiety provided one session of treatment to the participants. Four of them adopted the State-Trait Anxiety Inventory (STAI) form (Karst et al., 2007; Wang & Kain, 2001; Wang, Maranets, Weinberg, Caldwell-Andrews, & Kain, 2004; Wang, Peloquin, & Kain, 2001) and used an anxiety VAS as one of the outcome measures (Karst et al., 2007; Kober et al., 2003; Mora et al., 2007). The meta-analysis outcomes are presented in Figure 11. The synthesised results demonstrated that the real ear-acupuncture/ear-acupressure reduced more STAI scores (MD: -4.21, 95%CI: -7.14, -1.29) and anxiety VAS scores (SMD: -1.12, 95%CI: -2.13, -0.11) than the sham ear-acupuncture/ear-acupressure. However, the evidence of ear-acupuncture/ear-acupressure reducing anxiety VAS scores needs to be interpreted with cautious due to the high level of heterogeneity ($I^2= 88\%$). All seven studies used non-specific ear points in the sham control group (Type I). Only Karst (2007) applied fewer ear points in the sham group than in the real ear-acupuncture group.
a. Post-treatment STAI scores: real EAP versus sham EAP groups (Type I sham intervention)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karst 2007</td>
<td>43.53</td>
<td>9.99</td>
<td>19</td>
<td>45.21</td>
<td>10.82</td>
<td>19</td>
<td>19.5%</td>
<td>-1.68 [-8.30, 4.94]</td>
</tr>
<tr>
<td>Wang 2001b</td>
<td>38</td>
<td>9</td>
<td>31</td>
<td>40</td>
<td>14</td>
<td>27</td>
<td>22.6%</td>
<td>-2.00 [-8.16, 4.16]</td>
</tr>
<tr>
<td>Wang 2001b</td>
<td>35</td>
<td>8</td>
<td>32</td>
<td>40</td>
<td>14</td>
<td>27</td>
<td>24.1%</td>
<td>-5.00 [-10.96, 0.96]</td>
</tr>
<tr>
<td>Wang 2004</td>
<td>42.9</td>
<td>10</td>
<td>34</td>
<td>49.5</td>
<td>11</td>
<td>33</td>
<td>33.8%</td>
<td>-6.60 [-11.64, -1.56]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>116</td>
<td>106</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-4.21 [-7.14, -1.29]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)

b. Post-treatment anxiety VAS scores: real EAP versus sham EAP groups (Type I sham intervention)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karst 2007</td>
<td>3.03</td>
<td>2.16</td>
<td>19</td>
<td>3.21</td>
<td>2.74</td>
<td>19</td>
<td>33.2%</td>
<td>-0.07 [-0.71, 0.56]</td>
</tr>
<tr>
<td>Kober 2003</td>
<td>12.4</td>
<td>7.8</td>
<td>17</td>
<td>25.9</td>
<td>7.8</td>
<td>19</td>
<td>31.2%</td>
<td>-1.71 [-2.49, -0.93]</td>
</tr>
<tr>
<td>Mora 2007</td>
<td>15.4</td>
<td>9.8</td>
<td>50</td>
<td>28.9</td>
<td>9.8</td>
<td>50</td>
<td>35.5%</td>
<td>-1.58 [-2.03, -1.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>86</td>
<td>88</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.12 [-2.13, -0.11]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.70; Chi² = 16.51, df = 2 (P = 0.0003); I² = 88%
Test for overall effect: Z = 2.17 (P = 0.03)

Figure 11: Comparison of real and sham ear-acupuncture/ear-acupressure groups for anxiety
**Pain**

Among the trials on Pain using Type II sham control interventions (Alimi et al., 2003; Usichenko et al., 2005; Usichenko et al., 2007), two trials (Alimi et al., 2003; Usichenko et al., 2005) used pain intensity or modified pain intensity and two trials chose the use of analgesic medication as the outcome measures (Usichenko et al., 2005; Usichenko et al., 2007). The comparisons indicate that there were no significant differences between real and sham ear-acupuncture/ear-acupressure interventions in reducing pain intensity (MD: -4.56, 95%CI: -14.32, 5.20) or the use of analgesic medication (SMD: -0.42, 95%CI: -1.36, 0.51) when only trials using Type II sham control interventions were included, although a high level of heterogeneity was detected ($I^2 = 87\%$) when comparing real and sham ear-acupuncture/ear-acupressure for reducing the analgesic medication usage. However, when combined with the trial that used a Type III sham intervention (Wang, Hsu, Chien, Kao, & Liu, 2009), the real ear-acupuncture/ear-acupressure group became more effective in reducing pain intensity than the sham ear-acupuncture/ear-acupressure group (MD: -8.22, 95%CI: -15.05, 1.40) (see Figure 12a, b, c).
a. Post-treatment Pain Intensity: real EAP versus sham EAP groups (Type II sham intervention)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Real EAP</th>
<th>Sham EAP</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimi 2003</td>
<td>44</td>
<td>19</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td>Usichenko 2005</td>
<td>44</td>
<td>17</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>58</td>
<td>53</td>
<td>100.0%</td>
<td>-4.56 [-14.32, 5.20]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 19.63; Chi² = 1.65, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 0.92 (P = 0.36)

b. Post-treatment Pain Intensity: real EAP versus sham EAP groups (Type II & III sham interventions)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Real EAP</th>
<th>Sham EAP</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimi 2003</td>
<td>44</td>
<td>19</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td>Usichenko 2005</td>
<td>44</td>
<td>17</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>Wang 2009a</td>
<td>45.64</td>
<td>1.53</td>
<td>36</td>
<td>57</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>94</td>
<td>88</td>
<td>100.0%</td>
<td>-8.22 [-15.05, -1.40]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 22.36; Chi² = 4.98, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 2.36 (P = 0.02)

c. Post-treatment Use of Medication: real EAP versus sham EAP groups (Type II sham intervention)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Real EAP</th>
<th>Sham EAP</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usichenko 2005</td>
<td>0.44</td>
<td>0.22</td>
<td>29</td>
<td>0.67</td>
</tr>
<tr>
<td>Usichenko 2007</td>
<td>7.7</td>
<td>3.5</td>
<td>61</td>
<td>7.6</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>90</td>
<td>84</td>
<td>100.0%</td>
<td>-0.42 [-1.36, 0.51]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.40; Chi² = 7.84, df = 1 (P = 0.005); I² = 87%
Test for overall effect: Z = 0.89 (P = 0.37)

Figure 12: Comparison of real and sham ear-acupuncture/ear-acupressure groups for pain
Smoking

Three trials (Waite & Clough, 1998; White, Resch, & Ernst, 1998; Wu, Chen, Liu, Lin, & Hwang, 2007) investigated the effects of ear-acupuncture/ear-acupressure for smoking cessation using smoking cessation rate as the outcome measure. The synthesised results indicate that there are no differences between real and sham ear-acupuncture/ear-acupressure groups either for trials employing Type II sham intervention only (RR: 1.31, 95%CI: 0.62, 2.81) or when the Type I and Type II sham intervention studies are combined (RR: 1.27, 95%CI: 0.83, 1.96) (See Figure 13).
a. Post-treatment Smoking Cessation: real EAP versus sham EAP groups (Type II sham intervention)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Real EAP</th>
<th>Sham EAP</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waite 1998</td>
<td>15</td>
<td>7</td>
<td>38</td>
<td>43.4%</td>
<td>2.04 [0.93, 4.44]</td>
</tr>
<tr>
<td>White 1998</td>
<td>15</td>
<td>7</td>
<td>38</td>
<td>42.7%</td>
<td>0.94 [0.55, 1.61]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>78</td>
<td>76</td>
<td>100.0%</td>
<td>1.31</td>
<td>[0.61, 2.81]</td>
</tr>
</tbody>
</table>

Total events: 30, 23
Heterogeneity: Tau² = 0.19; Chi² = 2.62, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 0.70 (P = 0.48)

b. Post-treatment Smoking Cessation: real EAP versus sham EAP groups (Type I & II sham interventions)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Real EAP</th>
<th>Sham EAP</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waite 1998</td>
<td>15</td>
<td>7</td>
<td>38</td>
<td>43.4%</td>
<td>2.04 [0.93, 4.44]</td>
</tr>
<tr>
<td>White 1998</td>
<td>15</td>
<td>7</td>
<td>38</td>
<td>42.7%</td>
<td>0.94 [0.55, 1.61]</td>
</tr>
<tr>
<td>Wu 2007</td>
<td>16</td>
<td>12</td>
<td>59</td>
<td>32.5%</td>
<td>1.33 [0.69, 2.57]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>137</td>
<td>135</td>
<td>100.0%</td>
<td>1.27</td>
<td>[0.83, 1.96]</td>
</tr>
</tbody>
</table>

Total events: 46, 35
Heterogeneity: Tau² = 0.04; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%
Test for overall effect: Z = 1.10 (P = 0.27)

Figure 13: Comparison of real and sham ear-acupuncture/ear-acupressure groups for smoking cessation
4.3.3 Discussion

The findings of this recently updated systematic review show that four types of sham interventions have been used in RCTs of ear-acupuncture/ear-acupressure and the majority of studies used non-specific ear points or non-ear points in the sham control group.

The application of ear-acupuncture/ear-acupressure for different clinical conditions is increasing. Ear-acupuncture/ear-acupressure involves self-administration which differentiates itself from other types of therapies, such as acupuncture. Thus, the factors should be considered when designing a randomised, single-blinded, sham-controlled trial on ear-acupuncture/ear-acupressure, including point selection, manipulation and De Qi sensation. The treatment sessions should be also specified in the trial so that the outcomes from a trial can be implemented in the daily clinical practice.

As there are 93 acupoints on each ear (General Administration of Quality Supervision, & Inspection and Quarantine of the People's Republic of China, 2008), it is difficult to locate any non-ear points due to the small size of the ear. Particularly, the use of less number of ear points in the control group may tend to lead to positive results of the experimental intervention. It is preferred to have the equal number of ear points used in both groups which may make the single blinding possible.

Ear-acupuncture/ear-acupressure is a kind of microsystem acupuncture. Like acupuncture, De Qi sensation is critical for achieving the therapeutic effects (Frank & Soliman, 2006). In ear-acupuncture/ear-acupressure treatment, small press-stud acupuncture needles or ear pellets can be taped to the ear points and thus they can
remain on the ear points between the two visits to the clinicians. Consequently regular self-administered manipulation on the points becomes feasible. Continuous stimulation on the ear points may increase the therapeutic effects. Therefore, participants should be educated in the self-administration methods after the needles or pellets are placed on their ears. To achieve blinding, the same manipulation method should be taught to and applied by the participants from both experimental and control groups.

A different design is to answer a different research question. For example, to investigate which ear points should be chosen for treating a clinical condition, it may apply a same ear-acupuncture/ear-acupressure technique to specific and non-specific ear points. To examine the efficacy of an ear-acupuncture/ear-acupressure technique, the trial may use real and placebo ear-acupuncture/ear-acupressure techniques on the same ear points. To answer a question whether point localisation and skin penetration make a difference, the trial may use placebo needles on non-specific ear points in the sham control group. It is inappropriate to compare magnetic pellets with Semen Vaccariae seeds on the same points as the effects of Semen Vaccariae seeds have not been determined.

In conclusion, there are a number of different designs for sham interventions used in ear-acupuncture/ear-acupressure trials. Meta-analyses do not demonstrate a correlation between the sham intervention method and the results of the trial. When designing an RCT on ear-acupuncture/ear-acupressure, the control method should be designed carefully. To fulfil patients' blinding, equal number of points, same needling or pressing pellets with same stimulation should be employed. In consideration of the fact that it is difficult to locate any non-ear points due to the small
size of the ear, the “equal number of non-specific points method (type I) control method” seems to be the most common and credible method. In addition, it would make the result more reliable if the credibility of blinding is properly assessed during the RCT.
Chapter 5: General methodology of the ear-acupressure for allergic rhinitis clinical trial

Based on the findings from the two systematic reviews described in Chapter 4, the protocol of a randomised, single blinded, sham controlled clinical trial following a rigorous methodology was designed. The trial aimed to provide evidence for the efficacy and safety of ear-acupressure for the management of AR. The trial was conducted at two centres, and data were collected for different geographical locations and different ethnic groups. The two trial centres were: the Australian centre at RMIT University and the Chinese centre at Guangdong Provincial Academy of Chinese Medical Sciences, Guangdong Province, China.

The whole trial consists of three phases:

- Phase I: Pilot study I for testing the feasibility;
- Phase II: Pilot study II for testing the efficacy and sample size estimation;
- Phase III: The main trial.

Pilot study I (feasibility study) and Pilot study II (efficacy study) were conducted at the Australian trial centre while the main trial was conducted at both centres.

5.1 Trial aims and objectives

The aim of this clinical trial was to investigate whether ear-acupressure was effective in relieving AR symptom severity, improving AR sufferer’s quality of life, and reducing the usage of Western medicine in the management of AR. It also evaluated whether ear-acupressure was safe in the management of AR.
5.2 Trial design

This trial was designed as a randomised, single blinded, sham controlled, multi-centre trial using ear-acupressure to treat AR.

5.2.1 Randomisation

Randomisation numbers were generated by an independent statistician using Excel program. The numbers were randomly assigned to the real ear-acupressure or sham ear-acupressure group and sealed in individual opaque envelopes in blocks of 8, which were allocated by a central officer who was unaware of participants’ characteristics. To ensure the severity of the AR in the two groups was comparable, the randomisation was stratified based on the total nasal symptom score (TNSS). TNSS was calculated as the sum of the scores of four nasal symptoms (sneezing, blocked nose, runny nose, and itchy nose). The randomisation numbers generated for the TNSS 0-6 group and TNSS 7-12 group were kept in separate folders.

When participants came in for the first treatment visit, prior to the treatment the acupuncturist calculated the participants’ TNSS score according to four nasal symptom scores reported in the baseline case report forms (CRFs). Then each participant was asked to pick one sealed envelope which contained the randomisation number either from the TNSS 0-6 folder or from the TNSS 7-12 folder. The envelope was opened by the acupuncturist before the treatment. The randomisation number in the sealed envelope was used as participant’s code in the trial. The acupuncturist checked the participant’s code in the randomisation allocation table generated by independent statistician then delivered real or sham treatment accordingly.
5.2.2 Blinding

This study was designed as a single-blinded trial. In this study, only the acupuncturist knew which group the participants were assigned into as the acupuncturist was the person who performed the real and sham treatments. All other people involved in the study, including the participants, the personnel involved in recruitment, assessment, data entry and data analysis, were blinded.

5.2.3 Data management

5.2.3.1 Data collection

All data were collected using CRFs. Throughout the whole study, participants were required to record their AR symptom severity and other relevant information in their CRFs, during the run-in, treatment and follow-up periods. In all reports, participants were identified only by the code and initials rather than their names to protect their identity. Participants completing the CRFs, were required to always use a black ball-pen when writing, clearly state their participation code and initials on each page of the form and sign and date any changes that needed to be made.

5.2.3.2 Data handling

All data filled in the CRFs were the source data. Data entry was conducted by authorised independent research assistants involved in this project. Personnel who conducted data entry had received a training session on how to enter data prior to the commencement of the study. Data entry personnel did not know the group allocation of participants. A computer program (Excel) was used as the database to store all data. Data entry into the database was performed continuously throughout the study. Any corrections or changes of data were recorded. Double-checking was performed after entering data into databases to ensure accuracy of the data. The
data were stored in a password-protected computer and the database was secured by password to access.

All the record forms were filed in a locked cabinet during the trial and will be stored in the Chinese medicine clinical trial storage room at RMIT University for 15 years after publication. The records will then be shredded and disposed as required by the Therapeutic Goods Administration (TGA) (The Therapeutic Goods Administration, 2000).

5.2.4 Sample size

Pilot study I (feasibility study) included a small number of participants in order to test the trial design. Pilot study II (efficacy study) also included a small number of participants since it aimed to collect data to estimate the effect size for sample size calculation for the main trial. Upon the completion of the second pilot study, the sample size of the main trial was determined (Chapter 7, section 7.3.3).

5.3 Participant selection criteria

5.3.1 Inclusion criteria

According to the protocol, participants who met the following criteria were included in the study:

- Aged between 18 and 70 years (inclusive);
- A history of at least two years of typical symptoms of AR;
- Have a positive skin prick test to one or more of the following allergens: seven-grass mix, perennial rye, ragweed, dust mite, animal’s dander or mould;
- Currently not involved in other clinical trials for the treatment of AR;
• Agree to make themselves available for the period of the study; and
• Provide written consent for participation.

As discussed in Chapter 2, grass pollen, especially that of ryegrass, has been proven to be the major source of airborne allergens in Melbourne causing AR in the spring pollen season (Schappi et al., 1999). Therefore, for a trial scheduled in a pollen season (SAR trial), participants must have a typical seasonal pollen-induced AR history and a positive skin prick test result to any of the allergens of “seven-grass mix”, “ragweed” or “perennial ryegrass”. For the trial scheduled in non-pollen seasons (PAR trial), participants must have a typical PAR history and a positive skin prick test result to any of the allergens of “dust mite”, “animal’s dander” or “mould”, with or without a positive skin prick test to “seven-grass mix”, “ragweed” or “perennial ryegrass”.

5.3.2 Exclusion criteria

Participants with one or more of the following conditions were excluded from the study:

• Current systemic corticosteroid therapy;
• Other current active respiratory disease such as asthma;
• Nasal polyposis;
• Other structural defects of the upper respiratory tract;
• Wearing a hearing aid;
• History of being allergic to adhesive tape;
• History of HIV, Hepatitis B or C;
• Pregnancy;
- Have used ear-acupressure for respiratory diseases within the last six months;
- Do not read or understand English.

The exclusion criterion of wearing a hearing aid was included because wearing the hearing aid may interfere with the pellets attached to ear and change their location. People who are allergic to adhesive tape may not tolerate the pellets being attached to ear points using adhesive dressing, therefore, they were also excluded.

5.4 Recruitment and withdrawal of participants

5.4.1 Recruitment strategy

Trial participants were recruited through the media. Before recruiting, brief information about this trial was released to newspapers in the areas around the two trial sites, such as MX newspaper in the Melbourne CBD, Leader newspapers in the cities of Whittlesea, Manningham, Heidelberg, Diamond Valley, and Preston. Meanwhile, information on the trial was posted in University campuses and local clinics around Bundoora and Melbourne CBD areas. RMIT University media release promoted this trial on RMIT news via the RMIT update, RMIT student bulletin and RMIT alumni email. In addition, the information was put on the Google AdWords for one month. An example of the advertising poster is shown in Appendix A1.1.

During the recruitment, when volunteers made an enquiry and expressed their interest in this study through telephone or email, a brief introduction of this trial was provided and a short interview about the major selection criteria was conducted through telephone conversation. Once the volunteer’s condition was potentially eligible and she/he was willing to proceed with the study, a Plain Language
Statement (Appendix A1.2) was sent to this potential participant via email or mail to provide more detailed information about the trial. When the potential participants agreed to participate by signing informed consent forms (Appendix A1.3) after reading the Plain Language Statement, a recruiting questionnaire (Appendix A1.4 and A1.5) was sent to him/her to collect general information and other relevant information. Once the completed questionnaire had been returned, a preliminary screening was carried out according to the information provided in the questionnaire. All potentially eligible participants were invited to attend an initial assessment at the trial clinic, including a skin prick test (SPT), to enable a final decision regarding recruitment.

5.4.2 Initial assessment

The steps involved in the initial assessment are as follows:

a. Greeting and introduction by the investigators to the potential participants.

b. A detailed verbal explanation about the study was given and any questions from the participants were answered before seeking informed consent.

c. All participants were asked to provide informed consent in writing prior to other examinations. The informed consent forms consisted of two forms (Appendix A1.3):

- Prescribed Consent Form for Persons Participating in Research Projects Involving Tests and/or Medical Procedures.
- Prescribed Consent Form for Persons Participating in Research Projects Involving Interviews, Questionnaires or Disclosure of Personal Information.

Once signed off, a copy of the informed consent forms was given to the participants for their own record.
d. The allergen sensitivity skin prick test was carried out by a trained research assistant under close supervision by the same medical doctor. Allergens used in the skin prick tests were (Appendix A1.6):

- 7 grass mix (Kentucky bluegrass, Orchard grass, Redtop, Timothy, Sweet vernal grass, Meadow fescue and Perennial ryegrass),
- Perennial ryegrass,
- Ragweed,
- Dust mite,
- 10 mould mix [Alternaria tenuis, Hormodendrum cladosporioides, Phoma herbarum, Helminthosporium interseminatum, Aspergillus Mix (Aspergillus fumigatus, Aspergillus nidulans, Aspergillus niger, Aspergillus terreus), Penicilliun Mix (Penicillium digitatum, Penicillium expansum, Penicillium glaucum, Penicillium notatum, Penicillium roseum), Fusarium vasinfecctum, Rhizopus nigricans, Mucor racemosus, Pullularia pullulans],
- Cat hair,
- Dog hair.

All these test allergens were produced by Hollister-Stier Laboratories, Spokane, Washington, USA. For comparison, positive (histamine) and negative (saline) controls were also applied. The test was considered positive when the diameter of the wheal produced by an allergen was at least 3 mm larger than that of the negative control.

e. A physical examination was performed by a medical practitioner including the previous medical and allergy history, with special attention being paid to the examination of the nose (Appendix A1.7).
f. A registered Chinese medicine practitioner with more than 10 years’ clinical experience preformed the Chinese medicine differential diagnosis based on the principles described by the State Administration of Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine, 1995). The Chinese medicine differential diagnosis of AR is classified as four types: 1: Lung Deficiency; 2: Lung + Spleen Deficiency; 3: Lung + Kidney Deficiency; 4: Lung + Spleen + Kidney Deficiency (Appendix A1.8).

At the end of the initial assessment, decisions regarding inclusion or exclusion were made based on the results of the assessment according to the inclusion and exclusion criteria (Appendix A1.9). Then, baseline CRFs were provided to the included participants.

5.4.3 Withdrawal of participants

During the whole trial period, participants were free to withdraw at any stage of the trial without having to provide a reason to the investigators. The data of drop-outs were treated as missing data and the worst-case-scenario method was applied to the missing data when intention-to-treat analysis was conducted.

5.5 Process of the trial

5.5.1 Pilot study I (feasibility study) and the main trial

Pilot study I (feasibility study) and the main trial were conducted in non-peak pollen season. According to the protocol, pilot study I and the main trial lasted 22 weeks: a
two-week run-in period, an eight-week treatment period and a 12-week follow-up period.

5.5.1.1 Run-in period
Between the initial assessment and the eight-week treatment period, there was a two-week run-in period. During these two weeks, all included participants were asked to complete baseline CRFs to record their AR symptom severity, quality of life related to AR and their medication usage. They were also asked to record their opinion about ear-acupressure treatment in a validated credibility scale.

5.5.1.2 Treatment period
In the first visit to trial clinic, participants were randomised into either the real or sham ear-acupressure group. Subsequently, participants received either real or sham ear-acupressure treatments once a week for eight weeks. In each treatment, once the ear pellets were attached to the ear-points, participants were instructed on how to press the pellets to achieve therapeutic effects. In addition, participants were given guidance on how to ensure the pellets remain in place throughout the week. During the eight-week treatment period, participants were asked to complete the CRFs fortnightly (Pilot study I) or weekly (Pilot study II & main trial). Besides AR symptom severity, quality of life related to AR, their medication usage and opinion about ear-acupressure treatment, participants recorded the number of pellets remaining on their ear every day as a measure of dosage. In addition, participants were required to record unexpected adverse events, if any. In the CRFs for the first treatment week, there was one additional question about which group participants thought they were in to test the adequacy of blinding.
5.5.1.3 Follow-up period

All the participants with PAR were followed up for 12 weeks. After the ear-acupressure treatment ceased, participants were required to complete the CRFs once every four weeks. In the follow-up CRFs, all the information related to AR and ear-acupressure treatment was still recorded, except for the treatment dosage data. All the follow-up CRFs were sent back to the trial investigator by post.

The detailed procedure for clinic visits and CRF return during the 22-week trial period is summarised in Table 17.
Table 17: Summary of trial timing (Pilot study I and main trial)

<table>
<thead>
<tr>
<th>22 weeks</th>
<th>Trial timing</th>
<th>Pilot study I (feasibility study)</th>
<th>Main trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit clinic</td>
<td>CRF return</td>
<td>Visit</td>
<td>CRF return</td>
</tr>
<tr>
<td>Week 1</td>
<td>Baseline week 1</td>
<td>✓ Initial assessment</td>
<td>✓ Initial assessment</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Baseline week 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Treatment week 1</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Week 4</td>
<td>Treatment week 2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Week 5</td>
<td>Treatment week 3</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Week 6</td>
<td>Treatment week 4</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Week 7</td>
<td>Treatment week 5</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Week 8</td>
<td>Treatment week 6</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Week 9</td>
<td>Treatment week 7</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Week 10</td>
<td>Treatment week 8</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Week 11</td>
<td>Follow-up week 1</td>
<td>✓ CRF return by post</td>
<td>✓ CRF return by post</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>Follow-up week 2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 13</td>
<td>Follow-up week 3</td>
<td></td>
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<td>Week 14</td>
<td>Follow-up week 4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Week 15</td>
<td>Follow-up week 5</td>
<td>✓ CRF return by post</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 16</td>
<td>Follow-up week 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 17</td>
<td>Follow-up week 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 18</td>
<td>Follow-up week 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 19</td>
<td>Follow-up week 9</td>
<td>✓ CRF return by post</td>
<td>✓ CRF return by post</td>
<td></td>
</tr>
<tr>
<td>Week 20</td>
<td>Follow-up week 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 21</td>
<td>Follow-up week 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 22</td>
<td>Follow-up week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of week 22</td>
<td>End of trial</td>
<td>✓ CRF return by post</td>
<td>✓ CRF return by post</td>
<td></td>
</tr>
</tbody>
</table>
5.5.2 Pilot study II (efficacy study)

This pilot study was conducted in Melbourne’s peak pollen season. The participants included in this study suffered AR symptoms induced by pollens. Consequently, once the pollen season ends, these symptoms would be relieved as the pollen count falls off. There was no need to follow up after the pollen season ended. Therefore, this study lasted for ten weeks, including a two-week run-in period and an eight-week treatment period.

The detailed procedure of clinic visits and CRF return during the 10 week trial period is summarised in Table 18.

Table 18: Summary of trial timing (Pilot study II)

<table>
<thead>
<tr>
<th>10 weeks</th>
<th>Trial timing</th>
<th>Pilot study II (efficacy study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit clinic</td>
<td>CRF return</td>
</tr>
<tr>
<td>Week 1</td>
<td>Baseline week 1</td>
<td>✓ Initial assessment</td>
</tr>
<tr>
<td>Week 2</td>
<td>Baseline week 2</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Treatment week 1</td>
<td>✓</td>
</tr>
<tr>
<td>Week 4</td>
<td>Treatment week 2</td>
<td>✓</td>
</tr>
<tr>
<td>Week 5</td>
<td>Treatment week 3</td>
<td>✓</td>
</tr>
<tr>
<td>Week 6</td>
<td>Treatment week 4</td>
<td>✓</td>
</tr>
<tr>
<td>Week 7</td>
<td>Treatment week 5</td>
<td>✓</td>
</tr>
<tr>
<td>Week 8</td>
<td>Treatment week 6</td>
<td>✓</td>
</tr>
<tr>
<td>Week 9</td>
<td>Treatment week 7</td>
<td>✓</td>
</tr>
<tr>
<td>Week 10</td>
<td>Treatment week 8</td>
<td>✓</td>
</tr>
<tr>
<td>End of Week 10</td>
<td>End of trial</td>
<td>✓ CRF return by post</td>
</tr>
</tbody>
</table>

To monitor the pollen count, daily pollen count data were collected from September to December 2008 from the website provided by the School of Botany, Faculty of
Science, University of Melbourne. The detailed flow of the trial procedure is shown in Figure 14.

Figure 14: Detailed trial procedures
5.6 Real and sham ear-acupressure treatments

5.6.1 Treatment sessions

Based on our literature review, this trial was designed to provide ear-acupressure treatment once a week for eight weeks. In the eight-week treatment period, participants were invited to attend the trial clinic once a week to receive an ear-acupressure treatment. All treatments during the eight weeks were delivered by the same registered acupuncturist who had a five-year degree level training and over 10 years’ clinical experience in acupuncture. Each treatment session took 10 to 15 minutes. In the first treatment session, the acupuncturist explained the ear-acupressure technique to participants in detail before attaching the pellets to the ear points on one of the ears, and instructed participants about the proper method of maintaining adhesion of the pellets and stimulating the points during the treatment week. In the following treatment session, the acupuncturist removed the previous treatment pellets and attached new pellets on the other ear; participants returned the completed fortnightly CRF (Pilot study I) or weekly CRF (Pilot study II and main trial) and received a new CRF for the following two weeks (Pilot study I) or one week (Pilot study II and main trial).

5.6.2 Treatment process

In each treatment session, the participant was seated comfortably in an arm chair. The acupuncturist sterilised the skin surface of the ear with a commercial 70% isopropyl alcoholic skin cleansing swab, located the points with a detecting probe which had a round head that measured 1.2 mm in diameter then attached five pellets to the real or sham ear points of one of the participant’s ears. All the eight-week treatments started with using the left side ear. Once pellets were attached, the
acupuncturist gently pressed each pellet for about 10 seconds or until the ear became red or slightly sore. There was no skin penetration in the treatment. In the following treatment session, the other ear was selected for attaching pellets. Thus, the two ears were used alternately on a weekly basis. All participants were instructed by the acupuncturist to follow the same pressing technique and they were asked to press the five pellets three times a day regardless of real or sham group. The pressing technique was to promote the desired stimulation on the points in order to achieve the therapeutic effects.

5.6.3 Ear-acupressure pellets

The ear-acupressure treatment used commercial stainless steel press-pellet tapes (Migraine Pellets: Cat. No. PELSST S/Steel Tan, Acuneeds Co., Australia). The pellet measures 1.2 mm in diameter and is attached to a round adhesive tape 7 mm in diameter in a tan colour which is close to skin colour.

5.6.4 Ear-acupressure points selection

The real ear-acupressure points used in the RCT were selected according to the knowledge from the traditional literature, existing ear-acupressure for AR RCTs and experts’ opinions. Based on the review of the sham methods of ear-acupuncture/ear-acupressure treatment used in controlled trials (See Chapter 4, section 4.3), the method of sham ear-acupressure employed in this trial was to use non-specific points. The main reason for selecting this approach is the difficulty and lack of reliability of locating five non-therapeutic points near the real ear points. Considering that there are 93 points on the ear, the density of real points is high. Also the system of auricular therapy focuses more on zones of the ear rather than precisely located points. Consequently, for the sham control five non-allergy-specific ear points on the
helix were selected. Each of these is a real point so the sham control can be accurately replicated.

The ear points selected for this trial are as below:

5.6.4.1 Real ear-acupressure points

For the real treatment group, five specific ear points for AR were selected: Shenmen (TF₄), Internal Nose (TG₄), Lung (CO₁₄), Wind Stream (SF₁₂i) and Adrenal Gland (TG₂p). These five points were frequently used in other AR clinical trials (Zhang et al., 2010). Theoretically, Shenmen (TF₄) is considered to relieve stress and calm the mind; Internal Nose (TG₄) and Lung (CO₁₄) are used to relieve nasal symptoms; Wind Stream (SF₁₂i) and Adrenal Gland (TG₂p) target allergy relief (General Administration of Quality Supervision, & Inspection and Quarantine of the People’s Republic of China, 2008).

5.6.4.2 Sham ear-acupressure points

For the sham control group, another five non-AR-specific ear points on the helix were chosen: Helix 2 (HX₁₀), Shoulder (SF₄₅), Clavicle (SF₆), Occiput (AT₃), and Tooth (LO₁). These five points are not functionally related to the treatment of allergy or nose problems (General Administration of Quality Supervision, & Inspection and Quarantine of the People’s Republic of China, 2008).

The locations of the points are shown in Figure 15.
5.7 Diagnostic measures and outcome measures

Diagnostic data and treatment data were collected using participant self-assessment questionnaires. This section introduces all the instruments employed in the trial, including diagnostic measurement instruments and outcome measure instruments.

5.7.1 Diagnostic instruments used in the clinical trial

There were a number of questionnaires used in the recruiting procedure, including screening questionnaires:

5.7.1.1 Screening questionnaire

The screening questionnaire (Appendix A1.5) was designed to focus on collecting general information, the nature of participants’ complaint and questions related to the inclusion and exclusion criteria. This questionnaire was used to screen potential participants before they were considered for the initial assessment.
5.7.1.2 Skin prick test
The skin prick test was performed during the initial assessment of the trial (Appendix A1.6). It was conducted by a trained research assistant under close supervision by a medical doctor. Results were recorded on the skin prick test form and reviewed by the medical doctor for recruitment decision making (refer to 5.4.2 point d).

5.7.1.3 Clinical history and physical examination
This instrument was administered during the initial assessment by the Western medical doctor (Appendix A1.7). The purpose of this instrument was to collect general medical history with a focus on allergy history. The information obtained was utilised to confirm the diagnosis of AR in Western medicine and assist in the selection process by excluding participants with indications listed in the exclusion criteria (refer to 5.4.2 point e).

5.7.1.4 Chinese medicine questionnaire
The Chinese medicine questionnaire was administered during the initial assessment. This questionnaire was to determine the Chinese medicine differential diagnosis (Appendix A1.8). Diagnostic details of the tongue and pulse were collected by a registered Chinese medicine practitioner (refer to 5.4.2 point f).

5.7.2 Outcome measure instruments
According to the protocol, the outcome measures of this trial were:

- Nasal symptoms and non-nasal symptoms severity
- Quality of life questionnaire
- Medication usage
Participants’ opinion about ear-acupressure

Adverse event record

Data from outcome measures were collected through participant self-administered questionnaires. The instruments used for collecting primary and secondary outcome measures data are listed below:

5.7.2.1 Symptom severity and quality of life assessment

The AR symptom severity was the primary outcome measure. Two scales were employed to investigate the symptom severity, which were Juniper 4 point scale (Juniper et al., 2005) and Spector 7 point VAS (Spector et al., 2003). A symptom recording diary of the Juniper 4 point scale was applied to assist participants in making an accurate weekly assessment. In addition, a question about quality of life was included in the Spector 7 point VAS questionnaire.

Furthermore, participants’ quality of life related to AR was assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (in Pilot study I) or the Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) (in Pilot study II and main trial).

a. Juniper 4 point scale (Appendix A2.2 and Appendix A2.3)

The 4 point scale for symptom severity assessment used in this trial was adapted from the Clinical Outcomes and Adverse Effect Monitoring in AR reported by Juniper et al (Juniper et al., 2005). In this article, a 4 point scale (0, 1, 2, and 3) system was suggested to assess the four major nasal symptoms of AR, i.e., sneezing, stuffy/ blocked nose, runny nose and itchy nose. In our clinical trial, we included another 4 non-nasal symptoms in this assessment: itchy eyes, watery eyes, redness of eyes,
itchiness of ears and/or palate. TNSS was calculated as the sum of the scores of the four nasal symptoms (sneezing, blocked nose, runny nose, itchy nose). As each symptom can have values from 0 to 3, the lowest possible TNSS score is 0 while the highest TNSS is 12.

However, evaluating AR severity using these eight questions alone does not provide sufficient insight into the overall effects of the disease. Therefore, other questionnaires were also employed in this study.

**b. 7 point VAS (Spector et al., 2003) (Appendix A2.4)**

Details of this VAS instrument have been introduced in Chapter 2, section 2.10.1.2. This 7-point instrument contains VAS for assessing nasal symptom severity (individually for sneezing, running nose, congestion, itchy nose, and postnasal drip), non-nasal symptoms (individually for eye symptoms, throat symptoms, chronic cough, ear symptoms, headache and mental function), global assessment of overall nasal and non-nasal symptoms severity as well as global quality of life related to rhinitis severity (Spector et al., 2003). The scales used for assessment of the severity of each of the individual symptoms are: 1= none; 2= between 1 and 3; 3= mild; 4= between 3 and 5; 5= moderately bothersome; 6= between 5 and 7; 7= unbearably severe. The scales for assessing the global assessment of overall nasal and non-nasal symptoms severity as well as global quality of life related to rhinitis severity are with opposite scoring, which means, 1= unbearably severe and 7= none.

**c. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (Appendix A2.5) and Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) (Appendix A2.6)**
The RQLQ (Juniper & Guyatt, 1991) including 28 questions was employed to assess participants’ rhinitis-related quality of life. Participants were required to score those questions using a 7 point scale (0= not troubled; 1= hardly troubled at all; 2= somewhat troubled; 3= moderately troubled; 4= quite a bit troubled; 5= very troubled; 6= extremely troubled). The RQLQ(S) (Juniper, Thompson, Ferrie, & Roberts, 1999) is an updated and validated version of RQLQ. Instead of letting participants select their own activities, in RQLQ(S), three questions about activities are defined as "regular activities at home and at work", "social activities" and "outdoor activities" (more details refer to Chapter 2, section 2.10.2.2, Appendix A2.6).

In both the RQLQ and RQLQ(S) questionnaires, the 28 questions are clustered into seven domains: Activity domain, Sleep domain, Non nasal symptoms domain, Practical domain, Nasal symptoms domain, Eye symptoms domain and Emotional domain. The total score of symptoms in each domain was calculated for the 7 domains data analysis. As the number of questions included in each domain is different, the total score for each domain varies as listed in Table 19.

The total score of these seven domains were used for assessing the treatment effects.

Table 19: RQLQ seven domains’ total score

<table>
<thead>
<tr>
<th>Seven domains</th>
<th>Activity</th>
<th>Sleep</th>
<th>Non nasal symptoms</th>
<th>Practical</th>
<th>Nasal symptoms</th>
<th>Eye symptoms</th>
<th>Emotional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of questions</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>in each domain</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total score of each</td>
<td>0 - 18</td>
<td>0 - 18</td>
<td>0 - 42</td>
<td>0 - 18</td>
<td>0 - 24</td>
<td>0 - 24</td>
<td>0 - 24</td>
</tr>
</tbody>
</table>
5.7.2.2 Relief medication scores

Participants were permitted to use symptomatic relief medications and they were required to keep a record of their usage of relief medication during the trial using a standard form (Appendix A2.7). The use of anti-allergy relief medication is calculated as one point for each basic dose of tablet, eye drop or nasal spray. For example, a tablet of “Telfast 120mg” is calculated as 1 point, while a tablet of “Telfast 180mg” is 1.5 point. The total medication usage scores were calculated for data analysis as a secondary outcome measure.

5.7.2.3 Ear-acupressure dosage

Participants were required to record how many pellets were attached to ear points each day during the treatment period in a diary (Appendix A2.8). The total number of pellets each week was calculated to be the weekly dosage data for data analysis.

5.7.2.4 Participants’ opinion about ear-acupressure

Many therapy outcome investigations now employ some form of credibility and/or expectancy assessment to ensure initial equivalence among compared therapy conditions (Deviliya & Borkovecb, 2000). A validated questionnaire about participants’ opinion on the intervention was also employed in the CRFs in the present study (baseline, end of treatment and end of follow-up periods) (Appendix A2.10). This questionnaire consists of six questions related to expectancy and credibility, with a rating scale from 1 to 9 (Deviliya & Borkovecb, 2000).

5.7.2.5 Adverse event record

Participants were asked to record any unexpected feelings, signs and symptoms throughout the whole study period (treatment period and follow-up period) (Appendix
A2.9). When completing the adverse event form, participants were required to record when the event started; when the event stopped; the intensity of the unexpected feelings using the scale 1, 2 and 3 (1= mild, 2= moderate, 3= severe); the relationship between these feelings and the ear-acupressure was assessed as: 1= unrelated, 2= possibly, 3= probably, 4= definitely.

5.7.2.6 Credibility of blinding
To ensure the credibility of the blinding procedure for the real and sham ear-acupressure used in this study, a question about which group the participants thought they had been assigned into was employed in the first and last treatment weeks in the main trial (Appendix A2.10).

5.8 Data analysis
All data were processed and analysed by an independent statistician at RMIT University. The Statistical Package for the Social Sciences software version 18.0 for Windows (SPSS Inc., Chicago, USA) was used for data analysis. Baseline demographic characteristics such as gender and age were analysed by chi square test or t test to determine equivalence between the two groups. Variables showing baseline imbalance were taken into consideration when conducting data analysis (using the variables as covariates or performing sensitivity analysis to reveal the relationship between the variables and the outcome measures).

Intention-to-treat analysis was applied to outcome data to minimise bias due to withdrawals. Due to the fact that AR symptoms may reduce spontaneously along with the change of amount of airborne allergen, the worst-case-scenario method was
used in intention-to-treat data analysis, that is, all missing data were replaced by the highest score to represent the worst situation.

Data were presented as means, standard deviation (SD), standard error (SE), or 95% confidence interval (CI). Demographic information, pellets dosage, medication score and patients’ opinion data were reported as mean ± SD while symptom severity and quality of life outcome measures data were reported as mean ± SE. The mean differences between real and sham treatment groups were compared using Non-parametric Mann-Whitney Test. $P$ value $\leq 0.05$ was considered as statistically significant.
Chapter 6: Pilot study I (feasibility study)

This chapter presents the results of Pilot study I (feasibility study) conducted in 2008.

Upon approval of the trial protocol and the Ethics application by the RMIT Human Research Ethics Committee in November 2007 and registration with the Therapeutic Goods Administration (TGA) and the Australian New Zealand Clinical Trial Registry (ANZCTR) in March 2008, the pilot study was conducted at the Chinese Medicine Research Group, RMIT University, Bundoora West Campus following the trial protocol. The major purpose for conducting this pilot study was to test the methodology of this trial.

6.1 Methods

This pilot study was designed as a randomised, single blinded, sham-controlled trial. It was conducted in the non-pollen season in Melbourne (between May and November 2008). The whole study lasted 22 weeks including a two-week baseline, eight-week treatment and 12-week follow-up period. The details of the methods used in this pilot study have been discussed in Chapter 5. As mentioned, in this study, fortnightly CRFs were employed for data collection during the baseline and treatment periods. RQLQ which allowed participants to choose their three activities was used in all CRFs.
6.2 Results

6.2.1 Participants

Following advertising in the local newspaper in the Bundoora area, 81 volunteers showed interest in this study. Among them 28 volunteers were excluded due to not meeting the selection criteria; 35 volunteers could not participate because of time restrictions. Eventually 18 participants were included in the study and randomised into real (n= 10) and sham (n= 8) groups. One participant from the intervention group did not complete the treatment due to family reasons; three participants (one from the intervention group and two from the control group) failed to send back follow-up CRFs (Figure 16).
6.2.2 Demographic data and baseline characteristics of Pilot study I

Among all the included participants, the age ranged from 21 to 67 years old. The duration of PAR morbidity was between 2 and 36 years. The demographics in terms of age and gender of the two groups showed no statistically significant difference.

There was no significant difference between the two groups in: the number of current, previous and non-smokers; the duration of participants’ PAR morbidity; and whether
they had family history of AR. For the Chinese medicine differential diagnosis, only two participants were diagnosed as *Lung* Deficiency, the others were diagnosed as *Lung + Spleen*, *Lung + Kidney* or *Lung + Spleen + Kidney* Deficiency. Details are reported in Table 20.

Table 20: Demographics and baseline characteristics of included participants for Pilot study I

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n= 10)</th>
<th>Control (n= 8)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>36.30±11.42</td>
<td>47.38±16.20</td>
<td><em>t</em> = -1.927</td>
</tr>
<tr>
<td><strong>Duration of AR in years</strong></td>
<td>21.30±7.19</td>
<td>20.50±12.75</td>
<td><em>t</em> = 0.168</td>
</tr>
<tr>
<td><strong>Number of participants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>4</td>
<td><em>χ²</em> 1.8</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>0</td>
<td>1</td>
<td><em>χ²</em> 1.8</td>
</tr>
<tr>
<td>Former</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Has family history of AR</strong></td>
<td>3</td>
<td>4</td>
<td><em>χ²</em> 0.748</td>
</tr>
<tr>
<td><strong>Chinese Medicine Differentiation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung Deficiency</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lung + Spleen Deficiency</td>
<td>2</td>
<td>3</td>
<td><em>χ²</em> 0.99</td>
</tr>
<tr>
<td>Lung + Kidney Deficiency</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lung + Spleen + Kidney Deficiency</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

The results of the allergy skin prick tests show that most participants were allergic to more than one allergen and that the number of participants who were allergic to each allergen was not significantly different between the two groups (*p > 0.05*). Details are shown in Table 21.
Table 21: Skin prick test results of Pilot study I

<table>
<thead>
<tr>
<th></th>
<th>Number of participants who were positive to each allergen</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (n= 10)</td>
<td>Control group (n= 8)</td>
</tr>
<tr>
<td>Grass Mix</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Perennial Rye Grass</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Ragweed</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Mould Mix</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cat Hair</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Dog Hair</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dust Mite</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

Not all outcome measures between the two groups at baseline were comparable.

There were significant differences between the two groups in some of the symptom severity scales: Juniper 4 point Watery eyes ($p = 0.034$), Juniper 4 point redness of eyes ($p = 0.024$), Spector VAS congestion ($p = 0.018$), Spector VAS mental function ($p = 0.008$)) (Table 22). However, these differences may be caused by the very small sample size.
Table 22: Baseline and treatment effects for Pilot study I

a. Juniper 4 point symptom score

<table>
<thead>
<tr>
<th>Symptom severity</th>
<th>Baseline</th>
<th>End of treatment period</th>
<th>End of follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (n= 10) Mean±SE</td>
<td>Control group (n= 8) Mean±SE</td>
<td>Intervention group (n= 10) Mean±SE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total nasal symptom score</td>
<td>8.9±0.888</td>
<td>6.88±0.693</td>
<td>4.6±1.422</td>
</tr>
<tr>
<td></td>
<td>U=26.0 p= 0.209</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blocked nose</td>
<td>2±0.365</td>
<td>1.5±0.189</td>
<td>1.15±0.38</td>
</tr>
<tr>
<td></td>
<td>U=28.0 p= 0.261</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sneezing</td>
<td>2.3±0.26</td>
<td>2±0.267</td>
<td>1.25±0.352</td>
</tr>
<tr>
<td></td>
<td>U=31.0 p= 0.392</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Runny nose</td>
<td>2.6±0.221</td>
<td>1.88±0.398</td>
<td>1.2±0.351</td>
</tr>
<tr>
<td></td>
<td>U=24.5 p= 0.127</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itchy nose</td>
<td>2±0.298</td>
<td>1.5±0.267</td>
<td>1±0.387</td>
</tr>
<tr>
<td></td>
<td>U=28.0 p= 0.246</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>2±0.365</td>
<td>1.13±0.227</td>
<td>0.8±0.359</td>
</tr>
<tr>
<td></td>
<td>U=19.0 p= 0.053</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watery eyes</td>
<td>2.1±0.348</td>
<td>1±0.267</td>
<td>0.85±0.359</td>
</tr>
<tr>
<td></td>
<td>U=17.0 p= 0.034*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness of eyes</td>
<td>2±0.298</td>
<td>0.88±0.35</td>
<td>0.8±0.416</td>
</tr>
<tr>
<td></td>
<td>U=16.0 p= 0.024*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itchiness of ears and palate</td>
<td>1.2±0.327</td>
<td>1.13±0.35</td>
<td>0.8±0.389</td>
</tr>
<tr>
<td></td>
<td>U=38.0 p= 0.852</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: U: Mann-Whitney U test; *: p<0.05
b. Spector 7 point VAS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline</th>
<th>Significance</th>
<th>End of treatment period</th>
<th>Significance</th>
<th>End of follow-up period</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>(n= 10) Mean±SE</td>
<td>Control</td>
<td>(n= 8) Mean±SE</td>
<td>Intervention</td>
<td>(n= 10) Mean±SE</td>
</tr>
<tr>
<td>Sneezing</td>
<td>4.5±0.703</td>
<td>2.88±0.581</td>
<td>U=22.5 p= 0.116</td>
<td>3.1±0.71</td>
<td>2.88±0.451</td>
<td>U=39.0 p= 0.927</td>
</tr>
<tr>
<td>Runny nose</td>
<td>4.7±0.539</td>
<td>4.25±0.648</td>
<td>U=35.0 p= 0.649</td>
<td>3.2±0.668</td>
<td>3.06±0.593</td>
<td>U=40.0 p= 1</td>
</tr>
<tr>
<td>Congestion</td>
<td>5.5±0.522</td>
<td>3.38±0.42</td>
<td>U=14.0 p= 0.018*</td>
<td>3.05±0.736</td>
<td>2.56±0.538</td>
<td>U=36.0 p= 0.717</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>3.5±0.562</td>
<td>3.125±0.693</td>
<td>U=34.5 p= 0.619</td>
<td>2.7±0.688</td>
<td>2.13±0.375</td>
<td>U=38.5 p= 0.89</td>
</tr>
<tr>
<td>Post nasal drip</td>
<td>4.5±0.582</td>
<td>2.88±0.639</td>
<td>U=20.0 p= 0.072</td>
<td>2.8±0.668</td>
<td>2.63±0.541</td>
<td>U=37.5 p= 0.821</td>
</tr>
<tr>
<td>Total nasal symptoms</td>
<td>5.1±0.504</td>
<td>4.25±0.559</td>
<td>U=27.5 p= 0.247</td>
<td>3.15±0.679</td>
<td>3.25±0.62</td>
<td>U=37.0 p= 0.788</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>4.2±0.593</td>
<td>2.5±0.378</td>
<td>U=17.5 p= 0.042</td>
<td>2.5±0.687</td>
<td>2.31±0.4</td>
<td>U=38.0 p= 0.849</td>
</tr>
<tr>
<td>Throat symptoms</td>
<td>3.2±0.442</td>
<td>2±0.5</td>
<td>U=19.5 p= 0.060</td>
<td>2.55±0.66</td>
<td>2.19±0.526</td>
<td>U=39.5 p= 0.963</td>
</tr>
<tr>
<td>Chronic Cough</td>
<td>2.3±0.396</td>
<td>2.13±0.581</td>
<td>U=33.0 p= 0.51</td>
<td>1.9±0.586</td>
<td>2±0.509</td>
<td>U=38.0 p= 0.839</td>
</tr>
<tr>
<td>Ear symptoms</td>
<td>1.9±0.233</td>
<td>2.25±0.62</td>
<td>U=39.5 p= 0.963</td>
<td>2.05±0.634</td>
<td>2.06±0.563</td>
<td>U=34.5 p= 0.578</td>
</tr>
<tr>
<td>Headache</td>
<td>2.4±0.476</td>
<td>1.88±0.639</td>
<td>U=28.5 p= 0.261</td>
<td>2.3±0.638</td>
<td>1.19±0.132</td>
<td>U=27.0 p= 0.188</td>
</tr>
<tr>
<td>Mental function</td>
<td>3.8±0.533</td>
<td>1.75±0.526</td>
<td>U=11.0 p= 0.008*</td>
<td>2.2±0.616</td>
<td>2.25±0.62</td>
<td>U=39.0 p= 0.924</td>
</tr>
<tr>
<td>Global nasal and non-nasal symptoms</td>
<td>2.85±0.38</td>
<td>4.13±0.398</td>
<td>U=19.0 p= 0.054</td>
<td>4.95±0.594</td>
<td>4.31±0.559</td>
<td>U=29.0 p= 0.325</td>
</tr>
<tr>
<td>Global quality of life</td>
<td>2.3±0.3</td>
<td>3.5±0.327</td>
<td>U=15.0 p= 0.021</td>
<td>4.7±0.63</td>
<td>3.94±0.608</td>
<td>U=28.5 p= 0.303</td>
</tr>
</tbody>
</table>
### c. RQLQ 7 domains

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th></th>
<th>End of treatment period</th>
<th></th>
<th></th>
<th>End of follow-up period</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (n=10) Mean±SE</td>
<td>Control group (n=8) Mean±SE</td>
<td>Significance</td>
<td>Intervention group (n=10) Mean±SE</td>
<td>Control group (n=8) Mean±SE</td>
<td>Significance</td>
<td>Intervention group (n=10) Mean±SE</td>
<td>Control group (n=8) Mean±SE</td>
</tr>
<tr>
<td>Activities</td>
<td>10.5±1.855</td>
<td>6.65±2.058</td>
<td>U=36.5, p=0.349</td>
<td>8.9±2.268</td>
<td>10.25±0.901</td>
<td>U=38.5, p=0.894</td>
<td>7.06±2.159</td>
<td>8.63±2.195</td>
</tr>
<tr>
<td>Sleep</td>
<td>11.7±0.159</td>
<td>7.05±2.11</td>
<td>U=17.5, p=0.099</td>
<td>9.1±2.228</td>
<td>6.5±1.018</td>
<td>U=32.0, p=0.476</td>
<td>5.19±1.96</td>
<td>7.25±2.358</td>
</tr>
<tr>
<td>Non nose/eye symptoms</td>
<td>22.4±3.37</td>
<td>11.85±4.74</td>
<td>U=19.5, p=0.304</td>
<td>19.9±5.154</td>
<td>11±2.605</td>
<td>U=39.0, p=0.929</td>
<td>11.06±4.342</td>
<td>15.63±5.803</td>
</tr>
<tr>
<td>Practical</td>
<td>13.3±1.461</td>
<td>6.25±2.132</td>
<td>U=24.0, p=0.533</td>
<td>9.3±2.124</td>
<td>11.13±1.302</td>
<td>U=32.0, p=0.477</td>
<td>7.63±1.894</td>
<td>8.34±2.5</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>15.4±2.396</td>
<td>8.45±2.82</td>
<td>U=29.5, p=0.053</td>
<td>13.1±3.096</td>
<td>13.13±1.329</td>
<td>U=35.0, p=0.656</td>
<td>8.16±2.119</td>
<td>10.75±3</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>12.8±2.615</td>
<td>5.5±2.647</td>
<td>U=21.5, p=0.154</td>
<td>11.4±3.413</td>
<td>7.25±1.386</td>
<td>U=38.5, p=0.892</td>
<td>5.69±2.144</td>
<td>7.75±3.609</td>
</tr>
<tr>
<td>Emotional</td>
<td>13.3±2.098</td>
<td>6.75±2.594</td>
<td>U=28.5, p=0.211</td>
<td>12.5±3.277</td>
<td>9.88±1.38</td>
<td>U=39.5, p=0.964</td>
<td>6.56±2.65</td>
<td>8.25±3.5</td>
</tr>
</tbody>
</table>

Note: U: Mann-Whitney U test
6.2.3 Pellet dosage

In treatment week 2 and week 4, the pellet dosage in the real ear-acupressure group was lower than in the sham ear-acupressure group, while in week 6 and week 8, the difference between two groups reduced. There is no significant difference between the two groups in the total pellets dosage data for the eight weeks of the treatment period. There was no difference between real and sham intervention in terms of dosage ($p>0.05$). The results of pellet dosage are shown in Table 23.

**Table 23: Pellet dosage for Pilot study I**

<table>
<thead>
<tr>
<th>Intervention (n= 10) Mean±SD</th>
<th>Control (n= 8) Mean±SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortnightly total pellet dosage - week 1, 2</td>
<td>57.6±9.442</td>
<td>64.3±9.019</td>
</tr>
<tr>
<td>Fortnightly total pellet dosage - week 3, 4</td>
<td>59.7±6.961</td>
<td>64.5±7.616</td>
</tr>
<tr>
<td>Fortnightly total pellet dosage - week 5, 6</td>
<td>61.6±8.566</td>
<td>63.0±8.928</td>
</tr>
<tr>
<td>Fortnightly total pellet dosage - week 7, 8</td>
<td>60.2±9.355</td>
<td>61.3±11.997</td>
</tr>
</tbody>
</table>

6.2.4 Treatment effects for Pilot study I

Overall, the treatment effects for all outcome measures showed a trend of decrease in symptom severity and an increase in patients’ quality of life over the eight-week treatment period. The real ear-acupressure group achieved a greater trend compared with the sham ear-acupressure group in terms of most of the outcome measures. However, there was no significant difference between the two groups at the end of the eight-week treatment period or the twelve-week follow-up period ($p>0.05$) (Table 22, page 178). Examples are shown in Figure 17 and Figure 18.
6.2.5 Participants’ opinion about ear-acupressure for Pilot study I

In the two-week run-in period, the eight-week treatment and the 12-week follow-up period, the participants’ opinion about the ear-acupressure method for the two groups showed no significant difference ($p>0.05$) (Table 24).
Table 24: Participants’ opinion about ear-acupressure for Pilot study I

<table>
<thead>
<tr>
<th>Question</th>
<th>Baseline</th>
<th></th>
<th></th>
<th>End of treatment period</th>
<th></th>
<th></th>
<th>End of follow-up period</th>
<th></th>
<th></th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (n= 10) Mean±SD</td>
<td>Control group (n= 8) Mean±SD</td>
<td>Significance</td>
<td>Intervention group (n= 10) Mean±SD</td>
<td>Control group (n= 8) Mean±SD</td>
<td>Significance</td>
<td>Intervention group (n= 10) Mean±SD</td>
<td>Control group (n= 8) Mean±SD</td>
<td>Significance</td>
<td></td>
</tr>
<tr>
<td>Question 1</td>
<td>6±1.943</td>
<td>6.34±1.06</td>
<td>p= 0.632</td>
<td>6.6±2.503</td>
<td>5.31±2.251</td>
<td>p= 0.274</td>
<td>5.2±3.155</td>
<td>4±2.878</td>
<td>p= 0.417</td>
<td></td>
</tr>
<tr>
<td>Question 2</td>
<td>6.1±2.283</td>
<td>6.5±1.195</td>
<td>p= 0.661</td>
<td>6.5±2.494</td>
<td>4.81±2.725</td>
<td>p= 0.19</td>
<td>5.2±3.047</td>
<td>3.75±2.866</td>
<td>p= 0.319</td>
<td></td>
</tr>
<tr>
<td>Question 3</td>
<td>5.4±1.937</td>
<td>6.34±0.754</td>
<td>p= 0.313</td>
<td>6.35±2.625</td>
<td>5.25±2.493</td>
<td>p= 0.38</td>
<td>5.2±3.155</td>
<td>4±3.162</td>
<td>p= 0.435</td>
<td></td>
</tr>
<tr>
<td>Question 4</td>
<td>5.8±0.874</td>
<td>6.75±0.886</td>
<td>p= 0.207</td>
<td>6.05±2.455</td>
<td>4.94±2.859</td>
<td>p= 0.387</td>
<td>5.1±3.035</td>
<td>3.63±2.925</td>
<td>p= 0.313</td>
<td></td>
</tr>
<tr>
<td>Question 5</td>
<td>5.7±2.213</td>
<td>6.88±1.246</td>
<td>p= 0.2</td>
<td>6.4±2.355</td>
<td>4.88±2.167</td>
<td>p= 0.177</td>
<td>5.3±3.164</td>
<td>3.5±2.828</td>
<td>p= 0.227</td>
<td></td>
</tr>
<tr>
<td>Question 6</td>
<td>5.8±2.098</td>
<td>7.13±1.246</td>
<td>p= 0.135</td>
<td>6.05±2.409</td>
<td>4.63±2.722</td>
<td>p= 0.256</td>
<td>5.3±3.129</td>
<td>3.5±3.024</td>
<td>p= 0.236</td>
<td></td>
</tr>
</tbody>
</table>

Note: SD: Standard deviation.
Question 1: At this point, how logical does the treatment offered you seem?
Question 2: At this point, how useful do you think the treatment will be in reducing your hay fever symptoms?
Question 3: How confident would you be in recommending this treatment to a friend who experiences similar problems?
Question 4: By the end of the therapy period, how much improvement in your hay fever symptoms do you think will occur?
Question 5: At this point, how much do you really feel that therapy will help you to reduce your hay fever symptoms?
Question 6: By the end of the therapy period, how much improvement in your hay fever symptoms do you really feel will occur?
6.2.6 Medication score

Medication usage data in the two-week run-in period, at the end of eight-week treatment and the end of the twelve-week follow-up period showed no significant differences between the two groups ($p= 0.748, 0.273$ and $0.105$ respectively).

6.2.7 Adverse events

During the eight-week treatment period and the twelve-week follow-up period, all participants tolerated the ear-acupressure well and no adverse event related to the real or sham treatment was reported.

6.3 Discussion

In this pilot study, only one participant dropped out during the treatment period due to family reasons. The participants’ compliance with this trial was reliable. With regard to the pellet dosage, the real acupressure group’s dosage was lower than the sham group at the beginning of the trial and then became similar to that of the sham group. This was possibly caused by the different locations of the ear points in two groups. Once the real group participants became familiar with the pellets being attached to the ear points the pellets were less liable to fall off.

A trend of decreasing of symptom severity and increasing patient global quality of life was observed over the eight-week treatment period, however, it was not evident in the follow-up period (Figures 17 and 18, page 182). This suggested that ear-acupressure may have some short-term effects on the symptomatic relief of AR. Due
to the very small sample size of this pilot study, the conclusion of efficacy cannot be drawn reliable.

The major aim of conducting this pilot study was to test the methods used in this trial. Upon the completion of this pilot study, a few shortcomings of the study design were identified:

- Collecting data on participants’ symptom severity once every two weeks was not very reliable. When participants were filling in the fortnightly CRFs, their assessments of symptom severities usually were based on their memory of recent days.
- In the RQLQ questionnaire, three questions about activities let participants choose three most frequently affected activities in each CRF. However, these three activities were not consistent throughout the whole study as participants’ activities varied from day to day.
- Blinding credibility was not tested in this study.

Otherwise, the trial procedure regarding participant recruitment, conduct of the initial assessment, delivery of the treatment and data collection was feasible.

### 6.4 Conclusion

This pilot study showed that the trial protocol was feasible and that the ear-acupressure treatment might be effective and safe for the treatment of AR. The ear-acupressure methods were also well tolerated by patients. However, the sample size of this trial was too small to draw any conclusion. A larger size clinical trial was needed.
To ensure the accuracy of data collection in a further trial, a symptom severity diary was considered important and data collection should be more frequent than once every two weeks. Based on a suggestion from the author of the RQLQ questionnaires, RQLQ(S) should be employed in further studies to avoid the inconsistency in the activity assessment. In the RQLQ(S), the three questions about activities have been defined as:

1. Regular activities at home and at work (your occupation or tasks that you have to do regularly around your home);
2. Social activities (e.g. activities with your family and friends, playing with children and pets, sex, hobbies);
3. Outdoor activities (e.g. gardening, mowing the lawn, sitting outdoors, sports, going for a walk).

Finally, a credibility of blinding question is also necessary as effective blinding of participants to the treatment allocation reduces the risk of performance bias.

6.5 Minor changes to the protocol

Based on the findings from this pilot study, some minor changes were made to the original protocol:

I. A symptom diary was added to the CRFs. Participants were required to assess their overall symptom severity based on the symptom diary.
II. The fortnightly CRFs were changed to a weekly form in the run-in period and treatment period.
III. RQLQ questionnaire was replaced by the RQLQ(S) questionnaire.
IV. One question was added to ask participants about the credibility of blinding in a new form titled “Credibility of Blinding Questionnaire”. This question was
applied at the end of the first week and at the end of the eighth-week treatment period of the main trial.

The amended trial protocol was submitted to and approved by the RMIT Human Research Ethics Committee in August 2008.
Chapter 7: Ear-acupressure for allergic rhinitis Pilot study II  
(efficacy study)

Upon the completion of Pilot study I, the amendments for the trial protocol specified in Chapter 6 were submitted to and approved by the RMIT Human Research Ethics Committee in August 2008. Pilot study II (efficacy study) was conducted between September and December 2008 to investigate the efficacy of ear-acupressure for AR to provide data for sample size estimation for the main trial. This pilot study included 63 participants and was conducted at two sites: one site was located in the Melbourne CBD (RMIT University City campus) and another was in a suburb which was approximately 20 kilometres from the Melbourne CBD (RMIT University Bundoora West campus). As the period between September and December is Melbourne’s peak pollen season, participants with typical pollen induced AR were included in this pilot study.

7.1 Methods

This pilot study was conducted following the amended protocol. Details have been provided in Chapter 5. As discussed in Chapters 5 and 6, the outcome measures employed in this trial are: 4 point symptom score, 7 point VAS, RQLQ(S), medication usage related to AR and participants’ opinion about ear-acupressure treatment (Appendices A2.2, A2.3, A2.4, A2.6, A2.7, and A2.8). All the outcome measures data were collected from the participants’ self-assessments in the CRFs.

In addition, this pilot study was conducted during September and December 2008 (in the peak pollen season of Melbourne). In this season, patients may have severe AR symptoms during this short period, and afterwards their severe symptoms may
disappear spontaneously (Ong, Singh, & Knox, 1995). Therefore, due to the time restriction imposed by the duration of the pollen season, this trial lasted 10 weeks including two-week run-in period and eight-week treatment period. The twelve weeks follow-up period specified in the general protocol was not applied in this pilot study since this would extend the trial beyond the pollen season and into the time when seasonal rhinitis sufferers would be expected to recover spontaneously.

In the spring pollen season in Melbourne, from 1st September each year to 31st January the following year (considered as the peak pollen season), the School of Botany at the University of Melbourne and Asthma Victoria offer a service that forecasts the level of pollen in the air on a daily basis. The count is given as a quantitative assessment, on a scale from low to extremely high, and as actual values of the number of grass pollen grains per cubic meter of air/total number of all pollen types. For example, 30/105 means there were 30 grass pollen grains and 105 pollen grains of all types per cubic meter of air in the preceding 24-hour period.

7.2 Results

7.2.1 Participants

With media release and other recruiting strategies, 113 volunteers made enquiries and expressed their interest in this study. Thirty of them were excluded after the telephone interview or initial assessment due to not meeting the inclusion criteria, and 20 of them were not able to participate due to time restrictions. As a result, 63 volunteers were included in the trial and randomised into either real or sham ear-acupressure groups at a ratio of 1:1. Three in the real ear-acupressure group and three in the sham ear-acupressure group discontinued treatment, therefore, 28 in the
treatment group and 29 in the control completed the study. The details are presented in Figure 19.

Figure 19: Procedure of Pilot study II

7.2.2 Demographic data and baseline characteristics

Among all the included participants, the age ranged from 23 to 66 years old. The real ear-acupressure group had an average age of 39.97 years while the sham ear-acupressure group was 43.44 years. The demographics in terms of age and gender showed no significant differences ($p > 0.05$) between the two groups. There were no significant differences between the two groups in: number of participants who were current, previous or non smokers, the duration of participants’ AR morbidity, and whether they had a family history of AR. For the Chinese medicine differential
diagnosis, participants were diagnosed as belonging to all four syndrome categories: *Lung* Deficiency, *Lung + Spleen* Deficiency, *Lung + Kidney* Deficiency or *Lung + Spleen + Kidney* Deficiency with no statistical difference between the two groups (p>0.05). The demographics of the included participants were comparable (see Table 25).

**Table 25: Demographics and baseline characteristics of included participants of Pilot study II**

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n= 31)</th>
<th>Control (n= 32)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>39.97±11.51</td>
<td>43.44±10.74</td>
<td>t= -1.237</td>
</tr>
<tr>
<td>Duration of AR in years</td>
<td>20.06±13.17</td>
<td>19.84±12.48</td>
<td>t = 0.068</td>
</tr>
<tr>
<td><strong>Number of participants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>4</td>
<td>1</td>
<td>(\chi^2= 2.417)</td>
</tr>
<tr>
<td>Former</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Has family history of AR (n)</td>
<td>14</td>
<td>17</td>
<td>(\chi^2= 0.4)</td>
</tr>
</tbody>
</table>

The skin prick test results for allergy status in the two groups were comparable at baseline (\(p>0.05\)) (see Table 26).
Table 26: Skin prick test results for Pilot study II

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Intervention (n= 31)</th>
<th>Control (n= 32)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grass Mix</td>
<td>26</td>
<td>23</td>
<td>$\chi^2 = 1.311$</td>
</tr>
<tr>
<td>Perennial Rye Grass</td>
<td>26</td>
<td>26</td>
<td>$\chi^2 = 0.075$</td>
</tr>
<tr>
<td>Ragweed</td>
<td>21</td>
<td>25</td>
<td>$\chi^2 = 0.862$</td>
</tr>
<tr>
<td>Mould Mix</td>
<td>12</td>
<td>14</td>
<td>$\chi^2 = 0.165$</td>
</tr>
<tr>
<td>Cat Hair</td>
<td>17</td>
<td>19</td>
<td>$\chi^2 = 0.132$</td>
</tr>
<tr>
<td>Dog Hair</td>
<td>12</td>
<td>14</td>
<td>$\chi^2 = 0.165$</td>
</tr>
<tr>
<td>Dust Mite</td>
<td>27</td>
<td>24</td>
<td>$\chi^2 = 1.494$</td>
</tr>
</tbody>
</table>

The baseline data for the main outcome measures, Juniper 4 point symptom questionnaire, Spector 7 point VAS and RQLQ(S) were all comparable between the two groups ($p>0.05$) (see Table 27). The results for the end of the 8 week treatment phase are discussed in 7.2.5.
Table 27: Baseline and treatment effects for Pilot study II

a. Juniper 4 point symptom scores for Pilot study II

<table>
<thead>
<tr>
<th>Symptom severity</th>
<th>Baseline</th>
<th></th>
<th>End of treatment period</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group</td>
<td>Control group</td>
<td>Significance</td>
<td>Intervention group</td>
</tr>
<tr>
<td></td>
<td>(n= 31) Mean±SE</td>
<td>(n= 32) Mean±SE</td>
<td></td>
<td>(n= 10) Mean±SE</td>
</tr>
<tr>
<td>Total nasal symptom score</td>
<td>5.18±0.425</td>
<td>5.45±0.484</td>
<td>U= 537.00, p= 0.572</td>
<td>4.81±0.686</td>
</tr>
<tr>
<td></td>
<td>3.52±0.652</td>
<td>4.81±0.686</td>
<td></td>
<td>U= 606.50, p= 0.126</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1.34±0.176</td>
<td>1.29±0.155</td>
<td>U= 538.00, p= 0.956</td>
<td>0.87±0.178</td>
</tr>
<tr>
<td></td>
<td>0.87±0.178</td>
<td>1.25±0.18</td>
<td></td>
<td>U= 622.50, p= 0.102</td>
</tr>
<tr>
<td>Blocked nose</td>
<td>1.42±0.145</td>
<td>1.45±0.134</td>
<td>U= 492.00, p= 0.554</td>
<td>0.94±0.191</td>
</tr>
<tr>
<td></td>
<td>0.94±0.191</td>
<td>1.38±0.178</td>
<td></td>
<td>U= 608.50, p= 0.07</td>
</tr>
<tr>
<td>Runny nose</td>
<td>1.31±0.146</td>
<td>1.49±0.142</td>
<td>U= 561.00, p= 0.361</td>
<td>0.90±0.188</td>
</tr>
<tr>
<td></td>
<td>0.90±0.188</td>
<td>1.13±0.19</td>
<td></td>
<td>U= 558.50, p= 0.364</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>1.11±0.122</td>
<td>1.22±0.174</td>
<td>U= 516.50, p= 0.774</td>
<td>0.82±0.17</td>
</tr>
<tr>
<td></td>
<td>0.82±0.17</td>
<td>1.06±0.195</td>
<td></td>
<td>U= 553.50, p= 0.4</td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>0.94±0.135</td>
<td>1.25±0.151</td>
<td>U= 608.50, p= 0.116</td>
<td>0.74±0.193</td>
</tr>
<tr>
<td></td>
<td>0.74±0.193</td>
<td>1.06±0.185</td>
<td></td>
<td>U= 589.50, p= 0.168</td>
</tr>
<tr>
<td>Watery eyes</td>
<td>0.71±0.144</td>
<td>0.81±0.128</td>
<td>U= 549.50, p= 0.445</td>
<td>0.42±0.166</td>
</tr>
<tr>
<td></td>
<td>0.42±0.166</td>
<td>0.81±0.193</td>
<td></td>
<td>U= 613.50, p= 0.056</td>
</tr>
<tr>
<td>Redness of eyes</td>
<td>0.53±0.127</td>
<td>0.63±0.119</td>
<td>U= 546.00, p= 0.464</td>
<td>0.39±0.165</td>
</tr>
<tr>
<td></td>
<td>0.39±0.165</td>
<td>0.72±0.197</td>
<td></td>
<td>U= 584.50, p= 0.126</td>
</tr>
<tr>
<td>Itchiness of ears and palate</td>
<td>0.82±0.132</td>
<td>0.79±0.144</td>
<td>U= 471.00, p= 0.724</td>
<td>3.52±0.652</td>
</tr>
<tr>
<td></td>
<td>3.52±0.652</td>
<td>4.81±0.686</td>
<td></td>
<td>U= 581.50, p= 0.126</td>
</tr>
</tbody>
</table>

Note: U: Mann-Whitney U test; SE: Standard error.
### b. Spector 7 point VAS for Pilot study II

<table>
<thead>
<tr>
<th></th>
<th>Intervention group (n=31)</th>
<th>Control group (n=32)</th>
<th>Significance</th>
<th>Intervention group (n=10)</th>
<th>Control group (n=8)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SE</td>
<td>Mean±SE</td>
<td></td>
<td>Mean±SE</td>
<td>Mean±SE</td>
<td></td>
</tr>
<tr>
<td>Sneezing</td>
<td>2.71±0.244</td>
<td>3±0.266</td>
<td>U= 557.00, p= 0.398</td>
<td>2.19±0.336</td>
<td>3.281±0.376</td>
<td>U= 670.00, p= 0.013*</td>
</tr>
<tr>
<td>Runny nose</td>
<td>2.76±0.241</td>
<td>2.938±0.204</td>
<td>U= 560.50, p= 0.371</td>
<td>2.23±0.337</td>
<td>2.75±0.386</td>
<td>U= 567.00, p= 0.3</td>
</tr>
<tr>
<td>Congestion</td>
<td>3.11±0.3</td>
<td>2.672±0.241</td>
<td>U= 432.50, p= 0.379</td>
<td>2.29±0.325</td>
<td>2.97±0.361</td>
<td>U= 612.50, p= 0.097</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>2.31±0.191</td>
<td>2.703±0.278</td>
<td>U= 543.50, p= 0.508</td>
<td>2.10±0.336</td>
<td>2.69±0.377</td>
<td>U= 591.50, p= 0.159</td>
</tr>
<tr>
<td>Post nasal drip</td>
<td>2.21±0.246</td>
<td>2.344±0.245</td>
<td>U= 515.50, p= 0.784</td>
<td>1.97±0.352</td>
<td>2.66±0.4</td>
<td>U= 608.00, p= 0.077</td>
</tr>
<tr>
<td>Total nasal symptoms</td>
<td>3.10±0.245</td>
<td>3.141±0.218</td>
<td>U= 523.50, p= 0.703</td>
<td>2.16±0.344</td>
<td>3.10±0.369</td>
<td>U= 657.00, p= 0.02*</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>2.19±0.212</td>
<td>2.703±0.216</td>
<td>U= 618.00, p= 0.09</td>
<td>2.13±0.324</td>
<td>2.78±0.37</td>
<td>U= 604.00, p= 0.118</td>
</tr>
<tr>
<td>Throat symptoms</td>
<td>2.03±0.226</td>
<td>2.125±0.192</td>
<td>U= 544.50, p= 0.492</td>
<td>2.10±0.369</td>
<td>2.56±0.391</td>
<td>U= 567.50, p= 0.253</td>
</tr>
<tr>
<td>Chronic Cough</td>
<td>1.68±0.218</td>
<td>1.969±0.248</td>
<td>U= 540.00, p= 0.488</td>
<td>2±0.385</td>
<td>2.56±0.4</td>
<td>U= 597.50, p= 0.09</td>
</tr>
<tr>
<td>Ear symptoms</td>
<td>1.71±0.165</td>
<td>1.75±0.225</td>
<td>U= 467.50, p= 0.676</td>
<td>1.77±0.324</td>
<td>2.45±0.394</td>
<td>U= 603.50, p= 0.085</td>
</tr>
<tr>
<td>Headache</td>
<td>2.34±0.296</td>
<td>2.094±0.239</td>
<td>U= 482.50, p= 0.842</td>
<td>1.81±0.339</td>
<td>2.34±0.39</td>
<td>U= 584.50, p= 0.14</td>
</tr>
<tr>
<td>Mental function</td>
<td>2.16±0.259</td>
<td>1.984±0.18</td>
<td>U= 498.00, p= 0.977</td>
<td>1.81±0.329</td>
<td>2.38±0.401</td>
<td>U= 549.00, p= 0.368</td>
</tr>
<tr>
<td>Global nasal and non-nasal symptoms</td>
<td>4.37±0.241</td>
<td>4.313±0.243</td>
<td>U= 464.50, p= 0.663</td>
<td>5.39±0.33</td>
<td>4.41±0.364</td>
<td>U= 351.00, p= 0.042*</td>
</tr>
<tr>
<td>Global quality of life</td>
<td>4.26±0.191</td>
<td>4.406±0.208</td>
<td>U= 518.50, p= 0.755</td>
<td>5.39±0.337</td>
<td>4.56±0.351</td>
<td>U= 360.00, p= 0.056</td>
</tr>
</tbody>
</table>

Note: U: Mann-Whitney U test; SE: Standard error; *: p<0.05.
c. RQLQ 7 domains for Pilot study II

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline</th>
<th>Significance</th>
<th>End of treatment period</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (n=31) Mean±SE</td>
<td></td>
<td>Intervention group (n=31) Mean±SE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control group (n=32) Mean±SE</td>
<td>U= 498.50, p= 0.973</td>
<td>Control group (n=32) Mean±SE</td>
<td>U= 629.50, p= 0.062</td>
</tr>
<tr>
<td>Activities</td>
<td>7.79±0.662</td>
<td></td>
<td>4.26±1.01</td>
<td>7.41±1.078</td>
</tr>
<tr>
<td>Sleep</td>
<td>4.47±0.806</td>
<td></td>
<td>3.74±0.998</td>
<td>5.34±1.154</td>
</tr>
<tr>
<td>Non nose/eye symptoms</td>
<td>12.05±1.616</td>
<td>U= 525.50, p= 0.684</td>
<td>8.13±2.304</td>
<td>U= 598.00, p= 0.157</td>
</tr>
<tr>
<td>Practical</td>
<td>7.02±0.801</td>
<td>U= 523.00, p= 0.71</td>
<td>4.52±0.996</td>
<td>7.25±1.066</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>8.90±0.922</td>
<td>U= 494.50, p= 0.984</td>
<td>5.68±1.315</td>
<td>8.16±1.386</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>5.07±0.887</td>
<td>U= 546.00, p= 0.491</td>
<td>4.48±1.284</td>
<td>7.47±1.448</td>
</tr>
<tr>
<td>Emotional</td>
<td>7.29±1.022</td>
<td>U= 454.50, p= 0.568</td>
<td>5.23±1.327</td>
<td>7.78±1.482</td>
</tr>
</tbody>
</table>

Note: U: Mann-Whitney U test; SE: Standard error.
7.2.3 Pellet dosage

In treatment weeks 1 and 2, the weekly total pellet dosage in the real group was significantly lower than the weekly total dosage in the sham group (\( p = 0.008 \) and 0.017). From treatment weeks 3 to 8, the weekly total pellet dosage data of the real group and sham group were not significantly different (\( p > 0.05 \)). Details are listed in Table 28:

**Table 28: Pellet dosage for Pilot study II**

<table>
<thead>
<tr>
<th>Intervention (n= 31) Mean±SD</th>
<th>Control (n= 32) Mean±SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly total pellet dosage- week 1</td>
<td>30.16 ± 4.228</td>
<td>32.81 ± 3.345</td>
</tr>
<tr>
<td>Weekly total pellet dosage- week 2</td>
<td>29.45 ± 5.137</td>
<td>32.28 ± 3.937</td>
</tr>
<tr>
<td>Weekly total pellet dosage- week 3</td>
<td>32.87 ± 2.986</td>
<td>32.41 ± 3.5</td>
</tr>
<tr>
<td>Weekly total pellet dosage- week 4</td>
<td>32.10 ± 3.477</td>
<td>32.84 ± 3.184</td>
</tr>
<tr>
<td>Weekly total pellet dosage- week 5</td>
<td>33.32 ± 3.166</td>
<td>33.47 ± 3.016</td>
</tr>
<tr>
<td>Weekly total pellet dosage- week 6</td>
<td>33.32 ± 2.386</td>
<td>33.56 ± 3.141</td>
</tr>
<tr>
<td>Weekly total pellet dosage- week 7</td>
<td>33.58 ± 2.321</td>
<td>33.41 ± 3.151</td>
</tr>
<tr>
<td>Weekly total pellet dosage- week 8</td>
<td>33.16 ± 2.806</td>
<td>32.94 ± 3.809</td>
</tr>
</tbody>
</table>

Note: *: \( p < 0.05 \)

7.2.4 Pollen count data for Pilot study II

Pollen count data were obtained from the website of the School of Botany, University of Melbourne:


The daily pollen count was reported as grass/all kinds of pollen (grains per cubic metre of air) caught in the trap in the previous 24 hours. The average pollen count was calculated based on the daily pollen count report and is presented in Figure 20.
Figure 20: Average pollen count for Pilot study II

7.2.5 Treatment effects

As introduced in Chapter 5, the treatment effects were measured using three outcome measure instruments. By the end of the eight-week treatment, the real ear-acupressure group obtained a trend towards greater decrease in the severity of most symptoms compared with the sham ear-acupressure group (Appendix A3). This trend achieved via three questionnaires is consistent (Appendix A3). Detailed data for these three questionnaires are presented in Table 27 (Page 193).

7.2.5.1 Juniper 4 point symptom severity questionnaire

When nonparametric tests were applied to compare the results of the Juniper symptom severity questionnaire between the real and sham ear-acupressure groups, participants in the real ear-acupressure group obtained a trend towards less severe symptoms compared with the sham ear-acupressure group (Appendix A3.1).
However, no significant difference was found at the end of week 8 in terms of all the Juniper 4 point symptom scores, or TNSS ($p>0.05$) (Table 27a).

### 7.2.5.2 Spector 7 point VAS questionnaire at the end of treatment week 8

For the Spector 7 point VAS questionnaire, when comparing the scores between the real and sham ear-acupressure groups, significant differences at the end of week 8 were found in three of the scores (Table 27b, Appendix A3.2).

a. **Spector VAS Sneezing score**

The two groups’ sneezing scores for Spector VAS were comparable at baseline ($p=0.398$). At the end of the eight week treatment, the sneezing score in the real group was significantly lower than that in the sham group ($p=0.013$) Figure 21.

Note: *: $p<0.05$

**Figure 21: Spector VAS sneezing score for Pilot study II**
b. Spector VAS Total nasal symptoms score

The scores for total nasal symptoms for Spector VAS for the two groups were comparable at baseline ($p = 0.703$). A significant difference was obtained at the end of the treatment period ($p = 0.02$) in favour of the real group (Figure 22).

Note: *: $p < 0.05$

Figure 22: Spector VAS total nasal symptoms score for Pilot study II
c. Spector VAS global nasal and non-nasal symptom score

The global nasal and non-nasal symptom score for the Spector VAS is a reverse score. The lower the score is, the more severe symptom is. This scores for two groups were comparable at baseline ($p = 0.663$). At the end of treatment, the real group’s global nasal and non-nasal symptoms score was significantly higher than that in the sham group ($p = 0.042$) (Figure 23).

![Graph: Spector VAS Global Nasal and Non-nasal Symptom severity](image)

Note: *: $p< 0.05$

**Figure 23:** Spector VAS global nasal and non-nasal symptom severity score for Pilot study II

In the above figures, data are presented as Mean $\pm$ SE of the symptoms assessed at baseline and at the end of each treatment week. The real ear-acupressure group achieved significantly less symptom severity compared with the sham ear-acupressure group at the end of the eight-week treatment period in terms of sneezing ($p= 0.013$), total nasal symptoms ($p= 0.02$) and global nasal and non-nasal symptom scores ($p= 0.042$). No significant differences were obtained for the other symptoms ($p>0.05$) (Tables 27b).
Trends were evident in favour of the real group for other Spector VAS items (see Appendix A3.b). In particular there was a clear trend for a greater increase in global quality of life in the real group compared with the sham group (U = 360.00, p = 0.056) (Table 27b).

7.2.5.3 RQLQ(S) questionnaire 7 domains at the end of treatment week 8
Consistent with the Juniper 4 point and Spector 7 point VAS instruments, the results of RQLQ(S) questionnaire showed similar trends in favour of the real ear-acupressure group (Appendix A3.3). However, no significant differences between the two groups were found at the end of the treatment period for all seven domains (p > 0.05) (Table 27c).

Further analysis of the individual questions showed a significant difference for Regular activities at home and work (real ear-acupressure group 1.323±1.939 vs sham ear-acupressure group 2.031±1.992, p = 0.04) in the Activities domain.

7.2.6 Patients’ opinion about ear-acupressure
The six questions in the Patients’ opinion about ear-acupressure questionnaire asked how confident participants were regarding the possible treatment effects (Appendix 2.10). In the two-week run-in period, the participants’ opinion about ear-acupressure treatment between the two groups was not significantly different in terms of all six questions (p > 0.05). By the end of the eight weeks treatment period, there were significant differences between the two groups for five of the six questions:

- Question 2: “At this point, how useful do you think the treatment will be in reducing your hay fever symptoms?”
• Question 3: “How confident would you be in recommending this treatment to a friend who experiences similar problems?”

• Question 4: “By the end of the therapy period, how much improvement in your hay fever symptoms do you think will occur?”

• Question 5: “At this point, how useful do you really feel the treatment will be in reducing your hay fever symptoms?”

• Question 6: “By the end of the therapy period, how much improvement in your hay fever symptoms do you really feel will occur?”

These significant differences indicate that at the end of the eight-week treatment period, the participants in the sham ear-acupressure group were less confident of a treatment effect from this technique compared with those in the real group. Details are listed in Table 29.

Table 29: Participants’ opinion about ear-acupressure for Pilot study II

<table>
<thead>
<tr>
<th>Question</th>
<th>Baseline</th>
<th>End of treatment period</th>
<th>Significance</th>
<th>Interm</th>
<th>Control group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interven</td>
<td>(n=31)</td>
<td>(n=32)</td>
<td>p=</td>
<td></td>
<td>(n=31)</td>
<td>p=</td>
</tr>
<tr>
<td>group</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
<td></td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5.52±1.651</td>
<td>5.45±1.907</td>
<td>0.889</td>
<td>5.39±2.704</td>
<td>4.625±2.791</td>
<td>0.276</td>
</tr>
<tr>
<td>2</td>
<td>5.39±1.308</td>
<td>5.41±1.634</td>
<td>0.959</td>
<td>5.55±2.767</td>
<td>3.969±2.857</td>
<td>0.03*</td>
</tr>
<tr>
<td>3</td>
<td>4.97±1.426</td>
<td>5.19±1.731</td>
<td>0.585</td>
<td>5.55±2.694</td>
<td>4.188±2.669</td>
<td>0.048*</td>
</tr>
<tr>
<td>4</td>
<td>5.37±1.418</td>
<td>5.66±1.757</td>
<td>0.488</td>
<td>5.48±2.755</td>
<td>3.781±2.636</td>
<td>0.015*</td>
</tr>
<tr>
<td>5</td>
<td>5.26±1.384</td>
<td>5.5±1.818</td>
<td>0.555</td>
<td>5.42±2.693</td>
<td>3.969±2.788</td>
<td>0.04*</td>
</tr>
<tr>
<td>6</td>
<td>5.13±1.565</td>
<td>5.52±1.725</td>
<td>0.356</td>
<td>5.61±2.825</td>
<td>3.844±2.653</td>
<td>0.013*</td>
</tr>
</tbody>
</table>

Note: *: p<0.05

7.2.7 AR related medication usage score

The sum of all AR related medications used in each week was calculated as the weekly medication usage score. Comparison of the medication usage scores
between the two groups, found no significant difference in the baseline period and at the end of the treatment period. Furthermore, the weekly antihistamine medication score between two groups also was not significantly different at baseline and at the end of treatment ($p>0.05$). Details are summarised in Table 30.

**Table 30: Medication score of Pilot study II**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Endpoint</th>
<th>Intervention (n= 31) Mean±SD</th>
<th>Control (n= 32) Mean±SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AR medication score</td>
<td>Baseline</td>
<td>3.06±4.308</td>
<td>3.00±5.828</td>
<td>$p= 0.965$</td>
</tr>
<tr>
<td></td>
<td>At the end of treatment period</td>
<td>0.86±2.206</td>
<td>1.02±3.300</td>
<td>$p= 0.831$</td>
</tr>
<tr>
<td>Antihistamine medication score</td>
<td>Baseline</td>
<td>1.27±1.875</td>
<td>1.35±2.785</td>
<td>$p= 0.857$</td>
</tr>
<tr>
<td></td>
<td>At the end of treatment period</td>
<td>0.5±1.527</td>
<td>0.46±2.022</td>
<td>$p= 0.878$</td>
</tr>
</tbody>
</table>

**7.2.8 Adverse events**

Some adverse events related to the ear-acupressure treatment were reported during the eight-week treatment period as shown in Table 31.

**Table 31: Summary of adverse events of Pilot study II**

<table>
<thead>
<tr>
<th>Events/Group</th>
<th>Intervention (n= 31)</th>
<th>Control (n= 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore on the ear with pellets attached</td>
<td>3 mild, 3 moderate</td>
<td>3 mild</td>
</tr>
<tr>
<td>Itchiness on the ear with pellets attached</td>
<td>3 mild, 2 moderate</td>
<td>7 mild, 1 moderate</td>
</tr>
<tr>
<td>Feels annoying to have pellets attached to the ear</td>
<td>2 moderate</td>
<td>1 mild</td>
</tr>
<tr>
<td>Feel embarrassed to have pellets attached to the ear</td>
<td>1 mild</td>
<td>0</td>
</tr>
<tr>
<td>Feel uncomfortable at wrist when pressing pellets</td>
<td>4 moderate</td>
<td>0</td>
</tr>
<tr>
<td>All adverse events reported in treatment period</td>
<td>7 mild, 11 moderate</td>
<td>11 mild, 1 moderate</td>
</tr>
<tr>
<td>Number of participants reported adverse events (n= )</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>
The proportion of participants who reported mild or moderate adverse events was not significantly different between the treatment and sham groups (29.0% vs. 21.9%, \( p = 0.51 \)). The most frequent events reported were soreness on the ear due to pressure (6 real and 3 sham treatment participants) and itchiness on the ear (4 and 3 participants respectively). Over the eight weeks treatment period, participants in the real group reported 18 adverse events (seven mild and 11 moderate) with 12 adverse events reported by the sham group (11 mild and one moderate). Most of these mild or moderate discomforts were reported early in the treatment stage and were short-term or effectively managed by refinement of the pressing techniques by participants, without any medical assistance being required. No severe adverse event was reported in either group.

### 7.2.9 Credibility of blinding

The credibility of blinding question which let participants guess which group they were assigned into was employed in treatment week 1’s CRF. There was no significant difference between the two groups in the credibility of blinding. Details are provided in Table 32.

**Table 32: Credibility of blinding for Pilot study II**

<table>
<thead>
<tr>
<th>Credibility of blinding</th>
<th>Number of participants guessing group assignment</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention (n= 31)</td>
<td>Control (n= 32)</td>
</tr>
<tr>
<td>Real</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Sham</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Not sure</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>32</td>
</tr>
</tbody>
</table>
7.3 Discussion and conclusion

This trial is a pilot study for evaluating the efficacy of ear-acupressure for SAR. The results of this trial demonstrated the usefulness of ear-acupressure treatment for the short-term symptomatic management of AR. The efficacy results of this trial were used for sample size estimation for the main trial.

7.3.1 Amended protocol

Pilot study I proved that the trial protocol was feasible. Pilot study II, the amended questionnaires were employed. Firstly, the symptom diary required participants to record their symptoms every day, then all the weekly symptom assessment questionnaires were completed based on the diary. This ensured the data recorded in the weekly CRFs were accurate. Secondly, the CRFs required participants to assess their symptoms on a weekly basis (rather than fortnightly as in Pilot study I), this also helped ensure all the data were recorded in the CRFs accurately. Thirdly, according to the suggestion from questionnaires’ developer (Juniper, personal communication, August, 2008), RQLQ was replaced by RQLQ(S). Therefore, the three questions about participants’ activity could be kept consistent throughout the whole study. Finally, the question on credibility of blinding asked participants to guess which group they were assigned into when they received the first treatment. Participants were required to make this judgement based on their own understanding about this treatment. The results of this test indicated that more than half of the participants were not sure which group they were in. Statistically, there was no difference between two groups in terms of this question so the blinding procedure was considered successful. This successful blinding proved that the sham ear-acupressure method employed in this trial was appropriate.
The completion of this pilot study verified that the amended protocol was better-established and could be applied to the main trial.

7.3.2 Interpretation of results

7.3.2.1 Efficacy

This study was conducted during the peak pollen season. In the pollen season, participants’ allergy symptoms are influenced by the pollen count. Therefore, to simply compare patient’s symptom severity before and after treatment does not reflect the treatment effectiveness. When comparing symptom severity between the groups, there were some findings that indicated that the effects of the real ear-acupressure treatment were greater than those of the sham treatment in this trial.

- Juniper 4 point symptom score

Comparison of the two groups’ individual symptom scores and TNSS did not achieve significant results, though there was a trend towards greater reduction in the real ear-acupressure group than in the sham group. This might be caused by the small sample size. Moreover, the 4 point scale (0, 1, 2, 3 system) might not be able to detect minor changes in symptom severity precisely.

- Spector 7 point VAS

Significant differences between the two groups at the end of the treatment period were obtained for three questions: sneezing, total nasal symptoms and global nasal and non nasal symptoms. This questionnaire employed a seven point VAS instead of the four point system (none, mild, moderate, severe), which gave participants more options to select from. Perhaps this allowed participants to assess their symptom severity more precisely.
• RQLQ(S) 7 domains

Consistently, the scores for all seven domains showed a greater reduction in the real ear-acupressure group than that in the sham ear-acupressure group during the treatment period, although significant difference was not found at the end of the treatment.

7.3.2.2 Safety

There were some adverse events related to the ear-acupressure treatment reported during the eight week treatment period. However, all the reported adverse events were discomfort feelings caused by the ear-acupressure technique or social discomforts. Once participants got used to having the ear-acupressure pellets or became familiar with this treatment, these discomforts could be managed.

This study demonstrated that ear-acupressure treatment was well tolerated by participants and was a safe method for the management of AR.

This pilot study was scheduled in Melbourne’s peak pollen season. Participants involved in this study were suffering from acute pollen-induced AR symptoms. Since a follow-up period was impractical, no conclusion can be drawn regarding the long-term effect of ear-acupressure on SAR.

7.3.3 Semi-self-administration of ear-acupressure

To administrate the ear-acupressure treatment, participants themselves were involved in providing the pressure by pressing the pellets regularly during the whole treatment week after clinic attendance. Ten minutes each time, once a week attendance did not cause much inconvenience, nor was it time consuming. When
pressing the pellets, participants controlled the pressure and time, and they were allowed to take off the pellets if any of them caused unbearable pain. This semi-self-administered method was expected to reduce the possibility of adverse events.

The loss or removal of ear pellets has been reported in other trials (White, Moody, & Campbell, 2007) and may have been a factor in the lack of a clinical outcome but it was not known whether the loss of one or more of the five pellets would have an impact on the outcome in this trial. The weekly pellet dosage in real group was significantly lower in the real group in treatment week 1 and week 2. This difference possibly was caused by the locations of different ear points used for real and sham treatment resulting in a greater likelihood of certain points becoming detached.

However, there was no difference between the two groups for the rest of the treatment weeks. This result suggests that once the participants became used to the treatment, maintenance of the ear pellets and the administration of pressure on the pellets compliance by participants was equivalent in both groups.

With regard to efficacy, an increasing divergence between the two groups is evident from week 3 onwards, so it is plausible that the reduced pellet dosage in the real groups during weeks 1 and 2 had an effect on efficacy.

### 7.3.4 Sample size calculation for the main trial

Using G. Power 3.0.5 Software, based on data gathered using the Spector 7 point VAS (Spector et al., 2003), after the eight-week treatment the effect size estimate for total nasal symptoms (the primary end-point of the pilot study) was 0.466 (post-treatment mean scores 2.161±1.917 and 3.094±2.085 for the real and sham ear-acupressure groups respectively, \( p = 0.02 \)). Aiming for 90% statistical power with a significance level of 5% (2-tailed), the required sample size was 98 participants per
group. Based on the literature, most studies have an expected drop-out rate of 15% to 20% (Magnusson, Svensson, Leirvik, & Gunnarsson, 2004). Therefore, we expected a dropout rate of up to 18%, thus, the sample size required would be 116 participants in each group with 232 in total (see Table 33).

**Table 33 Sample size calculation according to various effect size**

<table>
<thead>
<tr>
<th>Effect size estimate</th>
<th>Required sample size per group for 90% power and 5% level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>n = 235</td>
</tr>
<tr>
<td>0.40</td>
<td>n = 133</td>
</tr>
<tr>
<td>0.47</td>
<td>n = 116</td>
</tr>
<tr>
<td>0.50</td>
<td>n = 86</td>
</tr>
<tr>
<td>0.55</td>
<td>n = 71</td>
</tr>
<tr>
<td>0.60</td>
<td>n = 60</td>
</tr>
</tbody>
</table>

Subsequently, the main trial was conducted in Australia and China. The results of the main trial at the Australian site are reported in Chapter 8.

**7.3.5 Conclusion and recommendations**

In conclusion, ear-acupressure seemed to be an effective treatment for pollen induced AR with regard to relieving the severity of sneezing, total nasal symptoms and global nasal and non-nasal symptoms. Being a pilot study, however, the sample size of this study was small so a solid conclusion could not be drawn. A larger size trial with a follow-up period was needed to further investigate both the short-term and long-term efficacy and safety of ear-acupressure treatment for AR.
Chapter 8: Ear-acupressure for allergic rhinitis: main trial

Upon completion of two pilot studies (Chapters 6 and 7), the main trial of ear-acupressure for AR was conducted. This main trial was an adequately powered, international, multi-centre, single-blinded, randomised controlled trial. Two trial centres were located in Melbourne, Australia and Guangzhou, China. This chapter reports the results from the Australia trial centre. The main trial at the Australia centre was conducted in the years of 2009 and 2010. The trial recruiting and treatment period was scheduled in non-pollen season (between April and September); the follow-up period was ended at spring season (November). This part of trial recruited a total of 117 participants. Same as Pilot study II, the Australia centre main trial was conducted in two sites: Melbourne CBD (RMIT University City Campus) and Bundoora, a suburb approximately 20 kilometres from the Melbourne CBD (RMIT University Bundoora West Campus).

8.1 Methods

This trial was conducted according to the amended protocol (Chapter 6, section 6.5). As the timing of this trial avoided peak pollen season, participants who have typical perennial AR history and a positive skin prick test to dust mite, animal’s dander or mould were included in this trial. The trial lasted 22 weeks including a two-week run-in period, an eight-week treatment period and a 12-week follow-up period.

8.2 Results

8.2.1 Participants

Following the recruitment strategy provided in Chapter 5 (section 5.4.1), 231 volunteers were screened from enquiries. The telephone interview and initial
assessment excluded 56 volunteers due to not meeting inclusion criteria. Fifty-eight volunteers were not able to participate due to time constraint and hence 117 were included in the trial. They were randomised into either real (n= 58) or sham ear-acupressure group (n= 59) in the first week of treatment after the 2 weeks run-in period. During the eight-week treatment period, 8 participants in real ear-acupressure group and 9 in sham ear-acupressure group discontinued due to time restriction; during the follow-up period, 4 participants in real ear-acupressure group and 8 in sham ear-acupressure group lost contact and failed to send back the follow-up CRFs. As a result, 100 participants completed the treatment and 88 participants completed follow-up assessment. Details of the trial procedure are shown in Figure 24.
Figure 24: Procedure of the main trial
8.2.2 Demographic data and baseline characteristics for the main trial

The age range of the 117 participants included in this trial was from 21 to 70 years old. The average age of the real ear-acupressure group was 42.91±11.09 years while that of the sham ear-acupressure group was 43.47±12.51 years. There was no significant difference between the two groups with regard to age and gender ($p>0.05$). Nor was there any significant difference between the two groups in terms of the number of current, previous and non-smokers in the two groups, the duration of participants' AR morbidity and whether they had a family history of AR. For the four types of Chinese medicine differential diagnoses, no difference was found between the two groups. The demographics of the included participants were all comparable ($p>0.05$). Details are shown in Table 34.
Table 34: Demographics and baseline characteristics of included participants of the main trial

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n= 58)</th>
<th>Control (n= 59)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>42.91±11.09</td>
<td>43.47±12.51</td>
<td>t = -0.256, p = 0.798</td>
</tr>
<tr>
<td>Duration of AR in years</td>
<td>21.84±13.59</td>
<td>19.14±4.07</td>
<td>t = 1.059, p = 0.292</td>
</tr>
<tr>
<td>Number of participants</td>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Smoker status</td>
<td>Current</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Former</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>Has family history of AR (n)</td>
<td>26</td>
<td>19</td>
<td>( \chi^2 = 1.969, p = 0.186 )</td>
</tr>
<tr>
<td>Chinese Medicine Differentiation</td>
<td>Lung Deficiency</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Lung + Spleen Deficiency</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Lung + Kidney Deficiency</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Lung + Spleen + Kidney Deficiency</td>
<td>23</td>
<td>26</td>
</tr>
</tbody>
</table>

The skin prick test results in the two groups were also comparable (p>0.05), see Table 35.
Table 35: Skin prick test results for the main trial

<table>
<thead>
<tr>
<th></th>
<th>Number of participants who were positive to each allergen</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention (n= 58)</td>
<td>Control (n= 59)</td>
</tr>
<tr>
<td>Grass Mix</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>Perennial Rye Grass</td>
<td>48</td>
<td>14</td>
</tr>
<tr>
<td>Ragweed</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Mould Mix</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Cat Hair</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Dog Hair</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Dust Mite</td>
<td>50</td>
<td>52</td>
</tr>
</tbody>
</table>

Using the nonparametric Mann-Whitney test, the baseline outcome measure data were comparable except for three variables (watery eyes in the Juniper 4 point symptom score, total nasal symptoms and global nasal and non-nasal symptoms from the Spector 7 point VAS). Detailed baseline data are listed in Table 36 (page 217):

- Juniper 4 point symptom score

In the Juniper 4 point symptom score questionnaire, the real ear-acupressure group’s “watery eyes” symptom score was more severe than that in the sham ear-acupressure group (0.74±0.098 and 0.49±0.091, U= 1334.50, p= 0.029). Other symptoms and TNSS were all comparable (p>0.05).

- Spector 7 point VAS

In this questionnaire, the scores for “total nasal symptom” were significantly different between the two groups (U= 1313.00, p= 0.029). The real ear-acupressure group’s score was more severe than that of the sham ear-acupressure group (3.25±0.151 and 2.77±0.159). The score for “global nasal and non-nasal symptoms” also was not
comparable ($U = 1419.00, p = 0.042$). The real ear-acupressure group had a more severe score of 4.03±0.14 while sham ear-acupressure group’s score was 4.69±0.118. Other scores showed no significant difference at baseline ($p>0.05$).

- RQLQ(S) 7 domains baseline data

In this trial, all the RQLQ(S) 7 domains baseline data were comparable ($p>0.05$).
Table 36: Baseline and treatment effects for the main trial

a. Juniper 4 point symptom severity scores for the main trial

<table>
<thead>
<tr>
<th>Symptom severity</th>
<th>Baseline Intervention (n= 58) Mean±SE</th>
<th>Control (n= 59) Mean±SE</th>
<th>Significance</th>
<th>End of treatment period Intervention (n= 58) Mean±SE</th>
<th>Control (n= 59) Mean±SE</th>
<th>Significance</th>
<th>End of follow-up period Intervention (n= 58) Mean±SE</th>
<th>Control (n= 59) Mean±SE</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total nasal symptom score</td>
<td>4.90±0.248</td>
<td>4.46±0.32</td>
<td>U= 1468.00  p= 0.184</td>
<td>4.37±0.449</td>
<td>5.56±0.456</td>
<td>U= 1280.00  p= 0.018*</td>
<td>5.12±0.53</td>
<td>6.09±0.542</td>
<td>U= 1437.00  p= 0.131</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1.39±0.077</td>
<td>1.28±0.105</td>
<td>U= 1562.50  p= 0.404</td>
<td>1.21±0.12</td>
<td>1.54±0.122</td>
<td>U= 1351.00  p= 0.036*</td>
<td>1.36±0.136</td>
<td>1.63±0.135</td>
<td>U= 1441.50  p= 0.157</td>
</tr>
<tr>
<td>Blocked nose</td>
<td>1.39±0.103</td>
<td>1.36±0.108</td>
<td>U= 1651.00  p= 0.738</td>
<td>1.16±0.124</td>
<td>1.57±0.141</td>
<td>U= 1331.00  p= 0.031*</td>
<td>1.40±0.137</td>
<td>1.79±0.147</td>
<td>U= 1339.50  p= 0.05*</td>
</tr>
<tr>
<td>Runny nose</td>
<td>1.34±0.101</td>
<td>1.08±0.100</td>
<td>U= 1389.50  p= 0.074</td>
<td>1.17±0.126</td>
<td>1.38±0.138</td>
<td>U= 1517.00  p= 0.268</td>
<td>1.35±0.147</td>
<td>1.5±0.156</td>
<td>U= 1567.50  p= 0.508</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>0.81±0.09</td>
<td>0.79±0.098</td>
<td>U= 1658.00  p= 0.766</td>
<td>0.83±0.133</td>
<td>1.07±0.145</td>
<td>U= 1516.00  p= 0.256</td>
<td>1.02±0.153</td>
<td>1.27±0.158</td>
<td>U= 1461.00  p= 0.196</td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>0.83±0.101</td>
<td>0.65±0.095</td>
<td>U= 1479.00  p= 0.189</td>
<td>0.75±0.138</td>
<td>1.03±0.139</td>
<td>U= 1415.00  p= 0.083</td>
<td>1.01±0.151</td>
<td>1.35±0.159</td>
<td>U= 1419.50  p= 0.128</td>
</tr>
<tr>
<td>Watery eyes</td>
<td>0.74±0.098</td>
<td>0.49±0.091</td>
<td>U= 1334.50  p= 0.029*</td>
<td>0.66±0.138</td>
<td>0.90±0.146</td>
<td>U= 1500.00  p= 0.196</td>
<td>0.95±0.154</td>
<td>1.16±0.167</td>
<td>U= 1544.50  p= 0.415</td>
</tr>
<tr>
<td>Redness of eyes</td>
<td>0.50±0.102</td>
<td>0.5±0.091</td>
<td>U= 1643.50  p= 0.677</td>
<td>0.59±0.143</td>
<td>0.83±0.143</td>
<td>U= 1435.50  p= 0.08</td>
<td>0.85±0.157</td>
<td>1.24±0.167</td>
<td>U= 1393.50  p= 0.084</td>
</tr>
<tr>
<td>Itchiness of ears and palate</td>
<td>0.62±0.109</td>
<td>0.44±0.086</td>
<td>U= 1546.00  p= 0.324</td>
<td>0.69±0.146</td>
<td>0.81±0.14</td>
<td>U= 1533.00  p= 0.272</td>
<td>0.86±0.158</td>
<td>1.08±0.166</td>
<td>U= 1493.50  p= 0.252</td>
</tr>
</tbody>
</table>

Note: U: Mann-Whitney U test; *: p<0.05; SE: standard error
### b. Spector 7 point VAS for the main trial

<table>
<thead>
<tr>
<th>Symptom severity</th>
<th>Baseline</th>
<th>Intervention (n= 58) Mean±SE</th>
<th>Control (n= 59) Mean±SE</th>
<th>Significance</th>
<th>End of treatment period</th>
<th>Intervention (n= 58) Mean±SE</th>
<th>Control (n= 59) Mean±SE</th>
<th>Significance</th>
<th>End of follow-up period</th>
<th>Intervention (n= 58) Mean±SE</th>
<th>Control (n= 59) Mean±SE</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sneezing</td>
<td>2.76±0.156</td>
<td>2.44±0.137</td>
<td>U= 1491.50</td>
<td>p = 0.226</td>
<td>2.65±0.254</td>
<td>3.32±0.253</td>
<td>U= 1273.50</td>
<td>p = 0.014*</td>
<td>3.10±0.307</td>
<td>3.67±0.306</td>
<td>U= 1384.00</td>
<td>p = 0.092</td>
</tr>
<tr>
<td>Runny nose</td>
<td>2.87±0.172</td>
<td>2.41±0.142</td>
<td>U= 1367.00</td>
<td>p = 0.607</td>
<td>2.79±0.26</td>
<td>3.17±0.262</td>
<td>U= 1482.00</td>
<td>p = 0.197</td>
<td>3.19±0.309</td>
<td>3.55±0.317</td>
<td>U= 1526.50</td>
<td>p = 0.377</td>
</tr>
<tr>
<td>Congestion</td>
<td>2.77±0.16</td>
<td>2.70±0.179</td>
<td>U= 1617.50</td>
<td>p = 0.067</td>
<td>2.73±0.255</td>
<td>3.25±0.261</td>
<td>U= 1404.50</td>
<td>p = 0.087</td>
<td>3.17±0.296</td>
<td>3.72±0.308</td>
<td>U= 1450.00</td>
<td>p = 0.19</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>2.04±0.132</td>
<td>2.02±0.151</td>
<td>U= 1602.50</td>
<td>p = 0.543</td>
<td>2.19±0.267</td>
<td>2.76±0.268</td>
<td>U= 1307.00</td>
<td>p = 0.019*</td>
<td>2.66±0.313</td>
<td>3.28±0.325</td>
<td>U= 1367.50</td>
<td>p = 0.066</td>
</tr>
<tr>
<td>Post nasal drip</td>
<td>2.49±0.182</td>
<td>2.03±0.154</td>
<td>U= 1382.00</td>
<td>p = 0.067</td>
<td>2.21±0.265</td>
<td>2.78±0.29</td>
<td>U= 1463.00</td>
<td>p = 0.147</td>
<td>2.83±0.311</td>
<td>3.4±0.336</td>
<td>U= 1485.50</td>
<td>p = 0.25</td>
</tr>
<tr>
<td>Total nasal symptoms</td>
<td>3.25±0.151</td>
<td>2.77±0.159</td>
<td>U= 1313.00</td>
<td>p = 0.029*</td>
<td>2.71±0.252</td>
<td>3.44±0.244</td>
<td>U= 1216.00</td>
<td>p = 0.005*</td>
<td>3.10±0.300</td>
<td>3.81±0.296</td>
<td>U= 1326.00</td>
<td>p = 0.044*</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>2.14±0.139</td>
<td>1.98±0.144</td>
<td>U= 1495.00</td>
<td>p = 0.227</td>
<td>2.24±0.266</td>
<td>2.75±0.276</td>
<td>U= 1421.00</td>
<td>p = 0.09</td>
<td>2.7±0.307</td>
<td>3.35±0.323</td>
<td>U= 1397.00</td>
<td>p = 0.099</td>
</tr>
<tr>
<td>Throat symptoms</td>
<td>2.09±0.168</td>
<td>1.78±0.131</td>
<td>U= 1554.50</td>
<td>p = 0.371</td>
<td>2.28±0.267</td>
<td>2.49±0.286</td>
<td>U= 1648.00</td>
<td>p = 0.709</td>
<td>2.66±0.313</td>
<td>3.14±0.339</td>
<td>U= 1498.00</td>
<td>p = 0.273</td>
</tr>
<tr>
<td>Chronic Cough</td>
<td>1.73±0.16</td>
<td>1.68±0.132</td>
<td>U= 1687.00</td>
<td>p = 0.882</td>
<td>2.26±0.273</td>
<td>2.29±0.291</td>
<td>U= 1645.50</td>
<td>p = 0.682</td>
<td>2.5±0.316</td>
<td>3±0.343</td>
<td>U= 1498.50</td>
<td>p = 0.252</td>
</tr>
<tr>
<td>Ear symptoms</td>
<td>1.67±0.125</td>
<td>1.45±0.1</td>
<td>U= 1504.00</td>
<td>p = 0.202</td>
<td>2.08±0.268</td>
<td>2.22±0.278</td>
<td>U= 1666.00</td>
<td>p = 0.778</td>
<td>2.56±0.321</td>
<td>2.97±0.34</td>
<td>U= 1483.50</td>
<td>p = 0.223</td>
</tr>
<tr>
<td>Headache</td>
<td>1.75±0.146</td>
<td>1.85±0.14</td>
<td>U= 1522.50</td>
<td>p = 0.275</td>
<td>2.12±0.277</td>
<td>2.39±0.282</td>
<td>U= 1495.50</td>
<td>p = 0.178</td>
<td>2.54±0.315</td>
<td>3.14±0.343</td>
<td>U= 1477.00</td>
<td>p = 0.214</td>
</tr>
<tr>
<td>Mental function</td>
<td>1.86±0.138</td>
<td>1.84±0.157</td>
<td>U= 1613.00</td>
<td>p = 0.566</td>
<td>2.17±0.271</td>
<td>2.46±0.288</td>
<td>U= 1622.50</td>
<td>p = 0.587</td>
<td>2.6±0.311</td>
<td>3.24±0.337</td>
<td>U= 1474.50</td>
<td>p = 0.216</td>
</tr>
<tr>
<td>Global nasal and non-nasal symptoms</td>
<td>4.03±0.14</td>
<td>4.69±0.118</td>
<td>U= 1419.00</td>
<td>p = 0.042*</td>
<td>4.97±0.246</td>
<td>4.05±0.223</td>
<td>U= 1092.50</td>
<td>p = 0.001*</td>
<td>4.41±0.266</td>
<td>3.85±0.279</td>
<td>U= 1425.00</td>
<td>p = 0.148</td>
</tr>
<tr>
<td>Global quality of life</td>
<td>4.33±0.11</td>
<td>4.65±0.125</td>
<td>U= 1345.00</td>
<td>p = 0.102</td>
<td>5.05±0.242</td>
<td>4.27±0.234</td>
<td>U= 1170.00</td>
<td>p = 0.002*</td>
<td>4.47±0.267</td>
<td>3.93±0.279</td>
<td>U= 1420.00</td>
<td>p = 0.139</td>
</tr>
</tbody>
</table>
### c. RQLQ(S) 7 domains for the main trial

<table>
<thead>
<tr>
<th>Symptom severity</th>
<th>Baseline</th>
<th>End of treatment period</th>
<th>End of follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention (n= 58) Mean±SE</td>
<td>Control (n= 59) Mean±SE</td>
<td>Intervention (n= 58) Mean±SE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control (n= 59) Mean±SE</td>
</tr>
<tr>
<td></td>
<td>Significance</td>
<td>Significance</td>
<td>Significance</td>
</tr>
<tr>
<td>Activities</td>
<td>5.75±0.391  U= 1423.50 p= 0.116</td>
<td>4.89±0.776 U= 1202.00 p= 0.005*</td>
<td>6.27±0.895 U= 1409.00 p= 0.094</td>
</tr>
<tr>
<td>Sleep</td>
<td>4.02±0.482  U= 1544.00 p= 0.36</td>
<td>4.09±0.788 U= 1306.00 p= 0.024*</td>
<td>5.36±0.91 U= 1360.00 p= 0.05*</td>
</tr>
<tr>
<td>Non nose/eye symptoms</td>
<td>11.13±1.164  U= 1595.00 p= 0.527</td>
<td>9.22±1.857 U= 1402.50 p= 0.087</td>
<td>12.60±2.111 U= 1369.50 p= 0.059</td>
</tr>
<tr>
<td>Practical</td>
<td>6.83±0.502  U= 1372.00 p= 0.064</td>
<td>5.40±0.772 U= 1502.00 p= 0.25</td>
<td>6.61±0.888 U= 1465.00 p= 0.175</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>8.44±0.557  U= 1537.50 p= 0.344</td>
<td>7.15±0.952 U= 1242.50 p= 0.01*</td>
<td>9.06±1.116 U= 1456.50 p= 0.161</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>4.60±0.563  U= 1527.50 p= 0.315</td>
<td>4.86±1.04 U= 1520.50 p= 0.289</td>
<td>6.41±1.214 U= 1414.50 p= 0.1</td>
</tr>
<tr>
<td>Emotional</td>
<td>6.74±0.663  U= 1697.50 p= 0.941</td>
<td>6.04±1.051 U= 1421.00 p= 0.11</td>
<td>7.60±1.208 U= 1391.00 p= 0.076</td>
</tr>
</tbody>
</table>

Note: U: Mann-Whitney U test; *: p<0.05; SE: standard error
8.2.3 Pellet dosage

During the eight-week treatment period, participants were required to record the daily number of pellets remaining on their ears to provide dosage data. The sum of weekly total pellet dosage was calculated for dosage data analysis. In the early weeks of the treatment period, the weekly total pellet dosage in the real group was lower than the weekly total dosage in the sham group and there was a significant difference in week 2 (week 2, real group 31.741±4.918, sham group 33.398±2.449, \( p = 0.023 \)). From treatment week 3 to week 8, there were no significant differences in terms of weekly total pellet dosage between the real and sham groups. Details are listed in Table 37:

Table 37: Pellet dosage for the main trial

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n= 58) Mean±SD</th>
<th>Control (n= 59) Mean±SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly total pellets dosage - week 1</td>
<td>32.24±3.724</td>
<td>33±4.03</td>
<td>( p = 0.292 )</td>
</tr>
<tr>
<td>Weekly total pellets dosage - week 2</td>
<td>31.74±4.918</td>
<td>33.4±2.449</td>
<td>( p = 0.023 )</td>
</tr>
<tr>
<td>Weekly total pellets dosage - week 3</td>
<td>32.91±3.757</td>
<td>33.61±3.227</td>
<td>( p = 0.284 )</td>
</tr>
<tr>
<td>Weekly total pellets dosage - week 4</td>
<td>33.07±4.068</td>
<td>32.80±3.362</td>
<td>( p = 0.694 )</td>
</tr>
<tr>
<td>Weekly total pellets dosage - week 5</td>
<td>33.45±3.174</td>
<td>33.63±2.228</td>
<td>( p = 0.725 )</td>
</tr>
<tr>
<td>Weekly total pellets dosage - week 6</td>
<td>33.02±3.601</td>
<td>33.39±2.659</td>
<td>( p = 0.525 )</td>
</tr>
<tr>
<td>Weekly total pellets dosage - week 7</td>
<td>33.60±2.759</td>
<td>33.53±3.093</td>
<td>( p = 0.886 )</td>
</tr>
<tr>
<td>Weekly total pellets dosage - week 8</td>
<td>33.55±2.747</td>
<td>33.70±2.298</td>
<td>( p = 0.76 )</td>
</tr>
</tbody>
</table>

8.2.4 Treatment effects

By the end of the eight-week treatment period and at the end of the follow-up period, the symptom severity in the real ear-acupressure group was generally lower compared with the sham ear-acupressure group (Table 36, page 217). Furthermore,
all the significant treatment effect results at the end of treatment period and follow-up period are summarised in Table 38. Details are discussed below.
Table 38: Summary of significant results for the main trial

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Symptom severity</th>
<th>End of treatment period</th>
<th>End of follow-up period</th>
<th>Significance*</th>
<th>Effect size</th>
<th>Significance*</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention (n= 58) Mean ± SE</td>
<td>Control (n= 59) Mean ± SE</td>
<td>Intervention (n= 58) Mean ± SE</td>
<td>Control (n= 59) Mean ± SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juniper 4 points symptom severity score</td>
<td>Total nasal symptom score</td>
<td>4.37±0.449</td>
<td>5.56±0.456</td>
<td><em>p= 0.018</em></td>
<td>-0.97</td>
<td>5.12±0.53</td>
<td>6.09±0.542</td>
</tr>
<tr>
<td></td>
<td>Sneezing</td>
<td>1.21±0.12</td>
<td>1.54±0.122</td>
<td><em>p= 0.036</em></td>
<td>-0.27</td>
<td>1.36±0.136</td>
<td>1.63±0.135</td>
</tr>
<tr>
<td></td>
<td>Blocked nose</td>
<td>1.16±0.124</td>
<td>1.57±0.141</td>
<td><em>p= 0.031</em></td>
<td>-0.39</td>
<td>1.4±0.137</td>
<td>1.79±0.147</td>
</tr>
<tr>
<td>Spector 7 points VAS</td>
<td>Sneezing</td>
<td>2.65±0.254</td>
<td>3.32±0.253</td>
<td><em>p= 0.014</em></td>
<td>-0.57</td>
<td>3.10±0.307</td>
<td>3.67±0.306</td>
</tr>
<tr>
<td></td>
<td>Itchy nose</td>
<td>2.19±0.267</td>
<td>2.76±0.268</td>
<td><em>p= 0.019</em></td>
<td>-0.62</td>
<td>2.66±0.313</td>
<td>3.28±0.325</td>
</tr>
<tr>
<td></td>
<td>Total nasal symptoms</td>
<td>2.71±0.252</td>
<td>3.44±0.244</td>
<td><em>p= 0.005</em></td>
<td>-0.71</td>
<td>3.1±0.3</td>
<td>3.81±0.296</td>
</tr>
<tr>
<td></td>
<td>Global nasal and non-nasal symptoms</td>
<td>4.97±0.246</td>
<td>4.05±0.223</td>
<td><em>p= 0.001</em></td>
<td>0.56</td>
<td>4.41±0.266</td>
<td>3.85±0.279</td>
</tr>
<tr>
<td>RQLQ(S)</td>
<td>Activities domain</td>
<td>4.89±0.776</td>
<td>6.92±0.745</td>
<td><em>p= 0.005</em></td>
<td>-1.92</td>
<td>6.27±0.895</td>
<td>8.19±0.914</td>
</tr>
<tr>
<td></td>
<td>Sleep domain</td>
<td>4.09±0.788</td>
<td>6.02±0.825</td>
<td><em>p= 0.024</em></td>
<td>-2.39</td>
<td>5.36±0.91</td>
<td>7.75±0.964</td>
</tr>
<tr>
<td></td>
<td>Nasal symptoms domain</td>
<td>7.15±0.952</td>
<td>9.53±0.96</td>
<td><em>p= 0.01</em></td>
<td>-2.30</td>
<td>9.06±1.116</td>
<td>11.36±1.194</td>
</tr>
</tbody>
</table>

Note: U: *: p<0.05 by Mann-Whitney U test.
8.2.4.1 Juniper 4 point symptom score at the end of treatment period and follow-up period

By applying the nonparametric Mann-Whitney test to compare the real/sham ear-acupressure groups, significant differences were found for: Sneezing (U= 1351.00, \( p = 0.036 \)) and blocked nose (U= 1331.00, \( p = 0.031 \)) between the two groups, as well as for TNSS (U= 1280.00, \( p = 0.018 \)) at the end of the eight-week treatment period. At the end of the follow-up period, a significant difference between the two groups was observed for blocked nose (U= 1339.50, \( p = 0.05 \)).

Figures 25 to 33 show the scores of TNSS and all individual symptoms at the baseline, for each week of the 8 week treatment period and at three points during the follow-up period: Follow up 1 (4 weeks), Follow up 2 (8 weeks), Follow up 3 (12 weeks).
a. Total nasal symptom score (TNSS)

The TNSS was calculated as the sum score of four nasal symptoms (sneezing, blocked nose, runny nose, itchy nose). The weekly TNSS was comparable between the real and sham groups at baseline ($U = 1468.00, p = 0.184$). At the end of the eight-week treatment period, the TNSS of the real group was significantly lower than that of the sham group ($U = 1280.00, p = 0.018$). At the end of follow-up period, the TNSS from two groups showed no significant difference ($U = 1437.00, p = 0.131$) (Figure 25).

Note: *: $p < 0.05$

**Figure 25: Juniper TNSS for the main trial**
b. Sneezing score

Similar to the TNSS, the sneezing score did not show a significant difference between real and sham groups at baseline (U= 1468.00, \( p = 0.404 \)). A significant difference between the two groups in favour of the real group was evident at the end of the treatment period (U= 1351.00, \( p = 0.036 \)) but not at the end of the follow-up period (U= 1441.50, \( p = 0.157 \)) (Figure 26).

Note: *: \( p < 0.05 \)

**Figure 26: Juniper sneezing score for the main trial**
c. Blocked nose score

In terms of the blocked nose scores, there was no significant difference between the two groups at baseline (U= 1651.00, \( p = 0.738 \)). A significant difference in favour of the treatment group was obtained at the end of the treatment period (U= 1331.00, \( p = 0.031 \)) and at the end of the follow-up period (U= 1339.50, \( p = 0.05 \)) (Figure 27).

![Juniper Blocked nose](image)

**Note:** *: \( p < 0.05 \)

**Figure 27:** Juniper blocked nose score for the main trial
d. Runny nose score

The symptom scores for runny nose were comparable between the real and sham treatment groups at baseline ($U=1389.50, p=0.074$), at the end of the treatment period ($U=1517.00, p=0.268$) and at the end of the follow-up period ($U=1567.50, p=0.508$) (Figure 28).

![Juniper Runny nose score for the main trial](image)

**Figure 28:** Juniper runny nose score for the main trial
e. Itchy nose score

The itchy nose scores for the two groups were comparable at baseline (U= 1658.00, p= 0.766), at the end of the treatment period (U= 1516.00, p= 0.256) and at the end of the follow-up period (U= 1461.00, p= 0.196) (Figure 29).

![Juniper Itchy nose score for the main trial](image)

**Figure 29: Juniper itchy nose score for the main trial**
f. Itchy eyes score

There were no statistically significant differences between the two groups in terms of itchy eyes scores before and after treatment and at the end of the follow-up period (U= 1479.00, 1415.00 and 1419.50, \( p = 0.189, 0.083 \) and 0.196) (Figure 30).

![Juniper Itchy eyes score for the main trial](image)

**Figure 30: Juniper itchy eyes score for the main trial**
g. Watery eyes score

When comparing the scores for watery eyes between the two groups at baseline, the score for the real group was significantly higher than that of the sham group (U=1334.50, \( p = 0.029 \)). However, at the end of the treatment period and at the end of follow-up, there were no differences between the two groups (U= 1500.00 and 1544.50, \( p = 0.196 \) and 0.415) (Figure 31).

![Figure 31: Juniper watery eyes score for the main trial](image)

Note: *: \( p < 0.05 \)
h. Redness of eyes score

The scores for redness of eyes for the two groups were comparable at baseline, and were not significantly different at the end of treatment and the end of follow-up period (U= 1643.50, p= 0.677; U= 1435.50, p= 0.08; and U= 1393.50, p= 0.084) (Figure 32).

Figure 32: Juniper redness of eyes score for the main trial
i. Itchiness of ears and palate score

The scores for itchiness of ears and palate were comparable at baseline, the end of treatment and the end of the follow-up period (U= 1546.00, \( p = 0.324 \); U= 1533.00 \( p = 0.272 \), and U= 1493.50, \( p = 0.252 \)) (Figure 33).

![Figure 33: Juniper itchiness of ears and palate score for the main trial](image-url)
8.2.4.2 Spector 7 point VAS at the end of treatment period and follow-up period

When comparing the Spector 7 point VAS scales between the real and sham ear-acupressure groups by applying the nonparametric Mann-Whitney test, at the end of the treatment period significant differences between the two groups were obtained for: sneezing (U= 1273.50, \( p = 0.014 \)), itchy nose (U= 1307.00, \( p = 0.019 \)), total nasal symptoms (U= 1216.00, \( p = 0.005 \)), global nasal and non-nasal symptoms (U= 1092.50, \( p = 0.001 \)), global quality of life (U= 1170.00, \( p = 0.002 \)). At the end of the follow-up period, significant differences between two groups were found for total nasal symptoms (U= 1326.00, \( p = 0.044 \)).

The detailed scores for the Spector 7 point VAS from baseline to the end of the follow-up period are shown in Figures 34 to 47.
a. Spector VAS Sneezing score

The sneezing scores from Spector 7 point VAS for the two groups were comparable at baseline (U= 1491.50, $p= 0.226$) and at the end of follow-up period (U= 1384.00, $p= 0.092$). However, there was significant difference at the end of the treatment period (U= 1273.50, $p= 0.014$) (Figure 34).

Note: *: $p< 0.05$

**Figure 34: Spector VAS sneezing score for the main trial**
b. Spector VAS Runny nose score

When the runny nose scores were compared between the two groups, no significant difference was observed at baseline (U= 1367.00, \( p = 0.058 \)), the end of treatment (U= 1482.00, \( p = 0.197 \)) or the end of the follow-up period (U= 1526.50, \( p = 0.377 \)) (Figure 35).

![Figure 35: Spector VAS runny nose score for the main trial](image)
c. Spector VAS Congestion score

The congestion scores were not significantly different between the two groups at baseline ($U= 1617.50, p= 0.607$), the end of treatment ($U= 1404.50, p= 0.087$) or the end of the follow-up period ($U= 1450.00, p= 0.19$) (Figure 36).

Figure 36: Spector VAS congestion score for the main trial
d. Spector VAS Itchy nose score

Itchy nose scores were comparable at baseline (U= 1602.50, \( p = 0.543 \)). At the end of the eight-week treatment, the itchy nose score of the real group was significantly lower than that of the sham group (U= 1307.00, \( p = 0.019 \)). However, at the end of the follow-up period, no significant difference was obtained (U= 1367.50, \( p = 0.066 \)) (Figure 37).

Note: *: \( p < 0.05 \)

**Figure 37: Spector VAS itchy nose score for the main trial**
e. Spector VAS Post nasal drip score

The post nasal drip score was comparable at baseline ($U = 1382.00, p = 0.067$), the end of the treatment period ($U = 1463.00, p = 0.147$) and the end of the follow-up period ($U = 1485.50, p = 0.25$) (Figure 38).

![Figure 38: Spector VAS post nasal drip score for the main trial](image-url)
f. Spector VAS Total nasal symptoms score

At baseline, the Spector VAS total nasal symptoms score of the real group was significantly higher than that of the sham group (U= 1313.00, \( p = 0.029 \)). At the end of the treatment period, the score of the real group was significantly lower than that of the sham group (U= 1216.00, \( p = 0.005 \)). At the end of the follow-up period, the score of the real group was significantly lower than that of the sham group (U= 1326.00, \( p = 0.044 \)) as well (Figure 39).

Note: *: \( p < 0.05 \)

**Figure 39: Spector VAS total nasal symptoms score for the main trial**
g. Spector VAS Eye symptoms score

The Spector VAS eye symptoms scores showed no significant difference between the two groups at baseline (U= 1495.00, p= 0.227), the end of treatment period (U= 1421.00, p= 0.09) or the end of the follow-up period (U= 1397.00, p= 0.099) (Figure 40).

Figure 40: Spector VAS eye symptoms score for the main trial
h. Spector VAS Throat symptoms score

The Spector VAS throat symptoms scores of the two groups were comparable at baseline (\(U = 1554.50, p = 0.371\)), the end of the treatment period (\(U = 1648.00, p = 0.709\)) and the end of the follow-up period (\(U = 1498.00, p = 0.273\)) (Figure 41).

Figure 41: Spector VAS throat symptoms score for the main trial
i. Spector VAS Chronic cough score

The Spector VAS chronic cough scores also showed no significant difference between the two groups at baseline \((U= 1687.00, p= 0.882)\), the end of treatment period \((U= 1645.00, p= 0.682)\) and the end of follow-up period \((U= 1498.50, p= 0.252)\) (Figure 42).

![Figure 42: Spector VAS chronic cough score for the main trial](image-url)
j. Spector VAS Ear symptoms score

Similarly, the Spector VAS ear symptom scores showed no significant difference between the two groups at baseline ($U= 1504.00, \ p= 0.202$), the end of treatment period ($U= 1666.00, \ p= 0.778$) or the end of the follow-up period ($U= 1483.50, \ p= 0.223$) (Figure 43).

Figure 43: Spector VAS ear symptoms score for the main trial
k. Spector VAS Headache score

No significant difference was found between the two groups in terms of Spector VAS headache scores at the baseline (U= 1522.50, \( p = 0.275 \)), the end of treatment period (U= 1495.50, \( p = 0.178 \)) and the end of follow-up period (U= 1477.00, \( p = 0.214 \)) (Figure 44).

![Figure 44: Spector VAS headache score for the main trial](image-url)
I. Spector VAS Mental function score

The Spector VAS Mental function scores were comparable at the baseline (U= 1613.00, p= 0.566), the end of the treatment period (U= 1622.50, p= 0.587) and the end of the follow-up period (U= 1477.00, p= 0.216) (Figure 45).

Figure 45: Spector VAS mental function score for the main trial
m. Spector VAS Global nasal and non-nasal symptom score

The Spector VAS Global nasal and non-nasal symptoms scores is a reverse score. The real group’s score was significantly lower than that in sham group at the baseline (U= 1419.00, \( p = 0.042 \)). At the end of the treatment period, the real group’s score was significant higher than that in the sham group (U= 1092.50, \( p = 0.001 \)). However, no significant difference was observed at the end of the follow-up period (U= 1425.00, \( p = 0.148 \)) (Figure 46).

![Figure 46: Spector VAS global nasal and non-nasal symptoms score for the main trial](image)

Note: *: \( p < 0.05 \)

**Figure 46:** Spector VAS global nasal and non-nasal symptoms score for the main trial
n. Spector VAS Global quality of life score

The Spector VAS Global quality of life score is a reverse score as well. The two groups' Spector VAS Global quality of life scores were comparable at the baseline (U= 1345.00, p= 0.102). A significant difference was evident at the end of the treatment period (U= 1170.00, p= 0.002); however, there was no significant difference at the end of the follow-up period (U= 1420.00, p= 0.139) (Figure 47).

Note: *: p< 0.05

Figure 47: Spector VAS global quality of life score for the main trial
8.2.4.3 RQLQ(S) 7 domains at the end of treatment period and follow-up period

When comparing the scores for the 7 domains of the RQLQ(S) questionnaire between the real and sham ear-acupressure groups at the end of the treatment period by applying the nonparametric Mann-Whitney test, significant differences between the two groups in favour of the treatment group were obtained in: Activities domain (U= 1202.00, \(p= 0.005\)), Sleep domain (U= 1306.00, \(p= 0.024\)), and Nasal symptoms domain (U= 1242.50, \(p= 0.01\)). At the end of the follow-up period, a significant difference was observed in the Sleep domain (U= 1360.00, \(p= 0.05\)).

The detailed total scores for the RQLQ(S) 7 domains for the baseline, the treatment period and the follow-up period are illustrated in Figures 48 to 54:
a. RQLQ(S) Activities domain score

When comparing the activities domain scores between the two groups, the baseline data were comparable (U= 1423.50, \( p = 0.115 \)). A significant difference was observed at the end of treatment (U= 1202.00, \( p = 0.005 \)) but not at the end of the follow-up period (U= 1409.00, \( p = 0.094 \)) (Figure 48).

Note: *: \( p < 0.05 \)

**Figure 48: RQLQ(S) activities domain score for the main trial**
b. RQLQ(S) Sleep domain score

When comparing the sleep domain scores, the baseline data were comparable between the two groups (U= 1544.00, \( p = 0.36 \)). At the end of the treatment period and at the end of the follow-up period, the sleep domain scores of the real group were significantly lower than those of the sham group (U= 1306.00 and 1360.00, \( p = 0.024 \) and 0.05) (Figure 49).

Note: \( ^* \): \( p < 0.05 \)

**Figure 49: RQLQ(S) sleep domain score for the main trial**
c. RQLQ(S) Non nose/eye symptoms domain score

Non nose/eye symptoms domain scores showed no difference between the two groups at the baseline ($U= 1595.00, \ p = 0.527$), the end of treatment period ($U= 1402.50, \ p = 0.087$) or the end of the follow-up period ($U= 1369.50, \ p = 0.059$) (Figure 50).

![RQLQ(S) Non nose/eye symptoms domain score for the main trial](image)

**Figure 50: RQLQ(S) non nose/eye symptoms domain score for the main trial**
d. RQLQ(S) Practical domain score

The practical domain scores showed no difference between the two groups at the baseline (U= 1372.00, \( p = 0.064 \)), the end of treatment period (U= 1502.00, \( p = 0.25 \)) and the end of the follow-up period (U= 1465.00, \( p = 0.157 \)) (Figure 51).

![Figure 51: RQLQ(S) practical domain score for the main trial](image)

e. RQLQ(S) Nasal symptoms domain score

The baseline data of the nasal symptoms domain scores were comparable (U = 1537.50, \( p = 0.344 \)). At the end of treatment, the score for real treatment group was significantly lower than that of the sham group (U = 1242.50, \( p = 0.01 \)). However, no significant difference was found at the end of the follow-up period (U = 1456.50, \( p = 0.161 \)) (Figure 52).

Note: *: \( p < 0.05 \)

**Figure 52: RQLQ(S) nasal symptoms domain score for the main trial**
f. **RQLQ(S) Eye symptoms domain score**

The eye symptoms domain scores showed no significant difference between the two groups at the baseline (U = 1527.50, \( p = 0.315 \)), at the end of treatment (U = 1520.50, \( p = 0.289 \)) and at the end of the follow-up period (U = 1414.50, \( p = 0.1 \)) (Figure 53).

![RQLQ(S) Eye symptoms domain score](image)

**Figure 53: RQLQ(S) eye symptoms domain score for the main trial**
g. RQLQ(S) Emotional domain score

When comparing the emotional scores for the two groups, no significant difference was obtained at the baseline (U= 1697.50, \( p = 0.941 \)), the end of the treatment period (U= 1421.00, \( p = 0.11 \)) or the end of the follow-up period (U= 1391.00, \( p = 0.076 \)) (Figure 54).

![RQLQ(S) Emotional domain score for the main trial](image)

**Figure 54:** RQLQ(S) emotional domain score for the main trial
8.2.5 Participants’ opinion about ear-acupressure

There was a significant difference between the two groups for questions 6 and 3 using T-test:

- Question 6: “By the end of the therapy period, how much improvement in your hay fever symptoms do you really feel will occur?”

Participants’ mean response to this question from the sham group (5.35±1.737) was significantly higher than that from the real group (6.04±1.693), (p= 0.03). It shows that at baseline, the participants in the sham group had a higher expectation of a treatment effect. However, at the end of eight weeks treatment period, there was no differences between the two groups (p>0.05).

At the end of the follow-up period, a significant difference between the two groups was found for question 3:

- Question 3: “How confident would you be in recommending this treatment to a friend who experiences similar problems?”

The mean response to this question from the real group participants (4.64±2.667) was significantly higher than that from the sham group (3.63±2.525), (p= 0.037), indicating that at the end of the follow-up period, the participants in the real group had more confidence in this treatment than those in the sham group. See Table 39.
Table 39: Participants’ opinion about ear-acupressure for the main trial

<table>
<thead>
<tr>
<th>Question</th>
<th>Baseline</th>
<th>End of treatment period</th>
<th>End of follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (n= 58) Mean±SD</td>
<td>Control group (n= 59) Mean±SD</td>
<td>Significance</td>
</tr>
<tr>
<td>Question 1</td>
<td>5.33±1.81</td>
<td>5.78±1.529</td>
<td>p= 0.188</td>
</tr>
<tr>
<td>Question 2</td>
<td>5.35±1.896</td>
<td>5.69±1.435</td>
<td>p= 0.286</td>
</tr>
<tr>
<td>Question 3</td>
<td>5.30±2.154</td>
<td>5.81±1.972</td>
<td>p= 0.19</td>
</tr>
<tr>
<td>Question 4</td>
<td>5.45±1.954</td>
<td>5.92±1.524</td>
<td>p= 0.152</td>
</tr>
<tr>
<td>Question 5</td>
<td>5.35±1.78</td>
<td>5.90±1.659</td>
<td>p= 0.082</td>
</tr>
<tr>
<td>Question 6</td>
<td>5.35±1.737</td>
<td>6.04±1.693</td>
<td>p= 0.03*</td>
</tr>
</tbody>
</table>

Note: Note: *: p<0.05; SD: Standard deviation
Question 1: At this point, how logical does the treatment offered you seem?
Question 2: At this point, how useful do you think the treatment will be in reducing your hay fever symptoms?
Question 3: How confident would you be in recommending this treatment to a friend who experiences similar problems?
Question 4: By the end of the therapy period, how much improvement in your hay fever symptoms do you think will occur?
Question 5: At this point, how much do you really feel that therapy will help you to reduce your hay fever symptoms?
Question 6: By the end of the therapy period, how much improvement in your hay fever symptoms do you really feel will occur?
8.2.6 Medication score for medicines related to AR

The weekly scores for all AR related medications and for antihistamine medications were compared between the two groups at the baseline, at the end of the treatment period and at the end of the follow-up period. No significant differences were observed. Details are shown in Table 40.

Table 40: Medication scores for the main trial

<table>
<thead>
<tr>
<th>Medication</th>
<th>Endpoint</th>
<th>Intervention (n= 58) Mean±SD</th>
<th>Control (n= 59) Mean±SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AR medication score</td>
<td>Baseline</td>
<td>3.14 ± 5.504</td>
<td>5.33 ± 11.599</td>
<td>p= 0.195</td>
</tr>
<tr>
<td></td>
<td>At the end of treatment period</td>
<td>2.37 ± 5.752</td>
<td>1.93 ± 4.629</td>
<td>p= 0.674</td>
</tr>
<tr>
<td></td>
<td>At the end of follow-up period</td>
<td>4.18 ± 8.362</td>
<td>3.66 ± 8.818</td>
<td>p= 0.773</td>
</tr>
<tr>
<td>Antihistamine medication score</td>
<td>Baseline</td>
<td>2.45 ± 4.289</td>
<td>2.52 ± 5.499</td>
<td>p= 0.947</td>
</tr>
<tr>
<td></td>
<td>At the end of treatment period</td>
<td>0.91 ± 3.282</td>
<td>1.35 ± 4.362</td>
<td>p= 0.57</td>
</tr>
<tr>
<td></td>
<td>At the end of follow-up period</td>
<td>4.18 ± 8.362</td>
<td>3.66 ± 8.818</td>
<td>p= 0.773</td>
</tr>
</tbody>
</table>

8.2.7 Adverse events

There was no significant difference between the two groups in terms of the adverse events reported during the treatment period and the follow-up period (Table 41).
Table 41: Summary of adverse events for the main trial

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Intervention (n= 58)</th>
<th>Control (n= 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore on the ear with pellets attached</td>
<td>11 mild, 4 moderate</td>
<td>8 mild, 2 moderate</td>
</tr>
<tr>
<td>Pressed too hard, pricked skin</td>
<td>1 mild</td>
<td>1 mild</td>
</tr>
<tr>
<td>Ear points inflamed</td>
<td>1 mild</td>
<td>0</td>
</tr>
<tr>
<td>Itchiness on the ear with pellets attached</td>
<td>8 mild, 3 moderate</td>
<td>3 mild, 1 moderate</td>
</tr>
<tr>
<td>Feeling bothering with pellets on when need to wear ear plugs</td>
<td>1 mild</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 mild, 5 moderate</td>
<td>3 mild, 1 moderate</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 moderate</td>
<td>1 moderate</td>
</tr>
<tr>
<td><strong>All adverse events reported in treatment and follow-up period</strong></td>
<td><strong>23 mild, 13 moderate</strong></td>
<td><strong>15 mild, 5 moderate</strong></td>
</tr>
<tr>
<td><strong>Number of participants reported adverse events (n= )</strong></td>
<td><strong>17</strong></td>
<td><strong>21</strong></td>
</tr>
</tbody>
</table>

The proportion of participants who reported mild or moderate adverse events was not significantly different between the treatment and sham groups (29.0% vs. 21.9%, \( \chi^2 = 0.526, p = 0.468 \)). The most frequent events reported were soreness on the ear due to pressure (15 real and 10 sham treatment participants) and itchiness on the ear (11 and 4 participants respectively). All the adverse events reported by participants were during the eight-week treatment period. In total, participants in the real treatment group reported 36 adverse events (23 mild and 13 moderate) with 20 adverse events being reported by the sham group (15 mild and 5 moderate). These mild or moderate discomforts were short-term and were effectively managed by refinement of the pressing techniques by the participants, without any medical assistance being required. No severe adverse event was reported during the treatment and follow-up periods.
8.2.8 Credibility of blinding

The credibility of blinding question which allowed participants estimate which group they were assigned into was included in the treatment week 1 and week 8 CRFs. There was no significant difference between the two groups in the credibility of blinding. Details are in Table 42:

**Table 42: Credibility of blinding for the main trial**

<table>
<thead>
<tr>
<th>Credibility of blinding</th>
<th>Intervention (n= 58) Mean±SD</th>
<th>Control (n= 59) Mean±SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Real</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Not sure</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>Credibility of blinding</td>
<td>Real</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Not sure</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>49</td>
<td>49</td>
</tr>
</tbody>
</table>

8.3 Discussion

This main trial is investigated the efficacy and safety of ear-acupressure in the treatment of AR. Based on the literature review, the pilot studies and the main trial are the first single-blinded, sham-controlled RCTs on ear-acupressure for AR which attempted to meet the challenge of fulfilling the requirements of conventional RCT methodology. The results from the main trial suggest that ear-acupressure was an effective and safe therapy for treating AR.
8.3.1 Methodology

Methodological deficiencies in acupuncture and CHM studies are a major concern in clinical research (Ernst, 1994). As discussed in Chapter 4 (section 4.2), Systematic review 1 which was conducted prior to the trial concluded that the previous clinical studies on ear-acupuncture/ear-acupressure for AR (Gao, Zhang, Zhu, & Zhang, 2008; Huo, 2003; Kong, Ren, & Lu, 2006; Qi & Wang, 2008; Rao & Han, 2006; Wang, 2004; Ye, Luo, & Xia, 2008) suffered methodological flaws (Zhang et al., 2010). The main trial followed a rigorous methodology to avoid the methodological weaknesses evident in previous studies.

8.3.1.1 Randomisation

Randomisation numbers were generated by an independent statistician. The randomisation was stratified based on the TNSS score to ensure the severity of major symptoms in the two groups was comparable. However, some other symptom scores at baseline between two groups was not comparable (Juniper watery eyes, Spector total nasal symptom, and Spector Global nasal and non-nasal symptom, see Table 36, Page 217). Overall, the participants in real group had more severe symptoms compare with those in the sham group.

8.3.1.2 Blinding

Being derived from acupuncture, ear-acupressure is a physical stimulus that requires individualised point selection and stimulation. Hence, in the research on body acupuncture or ear-acupuncture/ear-acupressure, it is impossible to meet all the requirements of a double blind design (Lewith, 1994). Therefore a single blind design, in which the participants are unaware of whether they were receiving the real or sham treatment, was chosen. In this trial, except for the acupuncturist, all other
personnel were blinded including participants, the personnel who assessed the eligibility of the participants, those who performed the randomisation and the personnel who conducted the data entry and data analysis. The credibility of blinding test conducted at the end of the first treatment week and at the end of the eight-week treatment period in this trial demonstrated that the blinding of this sham method was successful and the participants were properly blinded. In contrast, in previous ear-acupuncture/ear-acupressure for AR RCTs (Gao, Zhang, Zhu, & Zhang, 2008; Huo, 2003; Kong, Ren, & Lu, 2006; Qi & Wang, 2008; Rao & Han, 2006; Wang, 2004; Ye, Luo, & Xia, 2008) there was no participant blinding as a sham control method was not involved in any of these studies (Chapter 4, section 4.2.3).

8.3.1.3 Drop-outs and intention-to-treat analysis

Participants were free to drop-out at any time during the whole trial. All cases were analysed using intention-to-treat method to minimise bias due to withdrawals, which means, all the participants who began the treatment were considered to be part of the trial regardless of whether he or she finished the study. In this study, given that participants’ AR symptom severity may increase or decrease along with the change of weather and environment, the commonly used last-observation-carried-forward method may not have appropriately reflected the natural history of the disease. Therefore, all missing data were dealt with using the worst-case-scenario method in the intention-to-treat analysis. None of the previous ear-acupuncture/ear-acupressure trials for AR RCTs employed intention-to-treat analysis, so the results of this main trial are more accurate and reliable.
8.3.1.4 Selection of control method

This study adopted the most commonly used sham method employed in previous ear-acupuncture/ear-acupressure RCTs (Chapter 4, section 4.3). Five non-specific ear acupoints were selected for the treatment in the sham group. Except for the points’ location, the pellets, the treatment procedure, the intensity of points’ stimulation and other relevant details were the same as in the real treatment. Thus, it was difficult for the participants to find out their treatment allocations. This approach resulted in effective blinding and reduced bias.

There are a number of other advantages of using this method. Firstly, since the points used in the control group are all real points, the acupuncturist has no difficulty in locating them and consequently the sham treatment can be performed as naturally as the real treatment. Secondly, the sham treatment can be clearly specified and is consequently readily reproducible in other trials.

8.3.1.5 Sample size

Inadequate sample size threatens the validity of the findings and this has been a common problem for clinical trials. None of the previous ear-acupuncture/ear-acupressure studies reported appropriate sample size estimations. In the main trial, the expected sample size was calculated based on the results from Pilot study II. Being a multi-centre study, this main trial targeted 116 participants in each group with 232 in total allowing for a dropout rate of up to 18% (Chapter 7, section 7.3.3). The Australian trial centre recruited 117 participants to fulfil the targeted sample size.
8.3.1.6 Symptom severity and quality of life instruments employed in this trial

This trial employed three validated instruments in the CRFs to record participants’ symptom severity and quality of life data including:

- Simple 4 point rating scale (Juniper et al., 2005)
- Spector 7 point VAS (Spector et al., 2003)
- RQLQ(S) (Juniper, Thompson, Ferrie, & Roberts, 1999)

The details of these three validated instruments have been provided in Chapter 5 (section 5.7.2.1). These instruments have been frequently employed in previous AR clinical studies in the English literature (Brinkhaus et al., 2004; Brinkhaus et al., 2008; Xue et al., 2007; Xue, Thien, Zhang, Da Costa, & Li, 2003; Ng et al., 2004; Matkovic et al., 2010). The questions in these three questionnaires comprehensively assessed all problems relevant to AR, such as individual and total nasal symptoms, non-nasal symptoms, mental function, overall quality of life assessment, participants’ sleep, practical problems and emotions. By applying these three questionnaires in the CRFs, the effectiveness of ear-acupressure could be investigated in more detail compared with most of the previous ear-acupuncture/ear-acupressure for AR RCTs which only used “Total effective rate” as their outcome measure (Gao, Zhang, Zhu, & Zhang, 2008; Huo, 2003; Kong, Ren, & Lu, 2006; Wang, 2004; Ye, Luo, & Xia, 2008) (see 4.2.3.2).

Thus, the rigorous methodology supports the reliability of the results of the main trial.

8.3.2 Efficacy

8.3.2.1 Summary of efficacy

This main trial demonstrated that ear-acupressure treatment was effective in controlling AR symptoms in the following aspects:
• Short-term effect (at the end of the eight-week treatment period)

The ear-acupressure treatment used in this trial was effective in controlling AR participants' symptoms including: total nasal symptoms, sneezing, blocked nose, itchy nose, watery eyes, global nasal and non-nasal symptoms; and in improving participants' quality of life in terms of the global quality of life, activity and sleep.

• Long-term effect (at the end of the 12-week follow-up period)

The long-term effects of the ear-acupressure treatment were: controlling the severity of total nasal symptoms, alleviating blocked nose, and improving participants’ sleep quality.

Although there were no statistical differences between groups for a number of outcome measures, there were no instances where the sham control was superior to the treatment group at the end of the treatment period or at the end of follow up. Moreover, there are numerous examples of trends in which the treatment group is consistently superior to control from treatment week 3 onwards but this does not reach significance at $p< 0.05$ (see Figure 29 as example). Similar trends were evident in Pilot II. There are a number of likely reasons for these trends not reaching significance.

Firstly, the overall symptom severity in participants was not high for any of the measures and for some symptoms the scores were very low (see Figure 29 as example). In such a situation, the ability of participants to detect a difference in their symptoms is reduced.

Secondly, it is notable that the severity of many symptoms (see Figures 25 to 46) tends to rise in the sham group over the treatment period. This suggests a
background seasonal effect was operating and it was only when this background effect was at its maximum that significant differences between groups were detectable. Another possibility is that the ear-acupressure effect is delayed and gradually increases over time so it becomes most apparent in week 8. The lack of a difference between groups in the early weeks of treatment would support such an interpretation. Also there appears to be a ‘washout’ effect during follow up (see Figures 25 to 54).

Thirdly, participants continued to use relief medications throughout the study and this is likely to have created a ceiling effect by preventing symptom severity rising too high in either group.

Fourthly, conservative statistical approaches (Non-parametric test and intention-to-treat with worst-case-scenario) were used so some real differences may not have been detected.

Both the direction of the statistical differences and the trends suggest that there was a real effect for the real acupressure group and that a larger number of statistical differences would have been obtained had the sample size been larger. In fact, the results of the main trial presented in this thesis were based on the data in Australia site only. It might make some of the results under-powered. Including the data from the China site would give sample sizes which would enhance the power of the combined study. Further data analysis will be conducted for finalising further publication once the data from both sites are combined.
8.3.2.2 Relationship between the efficacy and the point selection

In this trial, the five specific ear points used for AR are: Shenmen (TF₄), Internal Nose (TG₄), Lung (CO₁₄), Wind Stream (SF₁,₂i) and Adrenal Gland (TG₂p). Theoretically, Shenmen (TF₄) is considered to relieve stress and calm the mind; Internal Nose (TG₄) and Lung (CO₁₄) are used to relieve nasal symptoms; Wind Stream (SF₁,₂i) and Adrenal Gland (TG₂p) are used to non-specifically target allergy relief. Therefore, nasal symptoms such as sneezing, blocked nose, itchy nose and total nasal symptoms may be reduced by the function of the Internal Nose (TG₄) and Lung (CO₁₄) points. The sleeping quality’s improvement was possibly caused by the function of Shenmen (TF₄) point. None of the ear points were specific for eye symptoms, throat symptoms or cough.

8.3.2.3 Symptom control

Consistent with Pilot study II, this trial demonstrated that real ear-acupressure was more effective than sham ear-acupressure for alleviating some AR symptoms. During the treatment and follow-up periods, the symptom severity of most outcome measures increased in both groups due to the impact of the change of the season. Although this trial was conducted in the non-peak pollen season in Melbourne and the pollen count data is not provided during the period of February to August, as the entire trial period was 22 weeks, participants recruiting and the run-in period was scheduled in the winter season while the end of the treatment period and the follow-up period fell into the early spring season when pollen count was starting to rise. Given the fact that most PAR participants included in this trial are allergic to not only dust mite, mould or animal, but also pollen allergens and as a result, participants’ symptoms worsened when spring started. In the main trial, the symptoms in the sham ear-acupressure group were more severe compared with those in the real group in
terms of most of the outcomes which indicated that the real ear-acupressure treatment was more effective than the sham ear-acupressure treatment for the management of AR. For a condition like AR, the symptom severity may vary according to the change of climate or environment. The treatment efficacy cannot be precisely explained only by comparing the symptom severity before and after treatment, but by comparing the symptom severity between the real and sham groups.

Compared with previous acupuncture RCTs on AR, the main trial demonstrated similar efficacy for ear-acupressure treatment. For example, a sham-controlled acupuncture RCT for PER participants conducted in Hong Kong between November 2001 and August 2002 reported similar results in terms of rhinitis symptom scores (Ng et al., 2004). In this study, 72 children with PER were recruited. Participants received real or sham acupuncture twice weekly for eight weeks then followed by twelve weeks of monitoring. Four nasal symptoms’ severity was recorded using a 4 point scale. The overall rhinitis symptom severity scores in the real group at the baseline, the end of treatment and the end of follow-up period were 6.58±3.21, 5.25±3.57 and 5.43 ±3.94; while those in the sham group were 6.51±3.32, 6.44±3.33 and 7.19±3.96 respectively. Although the rhinitis symptom severity in the real group did not achieve significant decrease compared with the baseline, when the between group analysis was conducted, there was significant difference between the two groups at the end of the follow-up period (p= 0.03). The effect size of acupuncture in terms of the overall rhinitis symptoms severity at the end of treatment was MD: -1.19; 95%CI: -2.78, 0.40, while the effect size of ear-acupressure in this main trial in terms of the TNSS was MD: -1.19; 95%CI: -2.44, 0.06. In other words, this main trial proved that ear-acupressure has similar effects as to acupuncture on symptom control for
AR. It was inconsistent with the Xue et al., 2007 study of acupuncture for PAR which demonstrated that real acupuncture achieved greater symptom reduction comparing with sham acupuncture. In the Xue et al., 2007 study, the symptom reduction induced by acupuncture does not seem to have any relationship with change of season. Whether this inconsistency is due to the different form of intervention or by different timing of trial conduct is yet to be confirmed. A pilot study (Fleckenstein et al., 2009) including 24 participants suggested that acupuncture was effective in reducing the nasal symptom score of vasomotor rhinitis. However, vasomotor rhinitis is not an allergic condition, the symptom severity does not vary along with the change of pollen count. Furthermore, the sample size of this study was relatively small to draw any conclusions.

8.3.2.4 Medication usage

This trial did not provide evidence of ear-acupressure treatment reducing allergic rhinitis participants’ anti-allergy medication usage related to allergic rhinitis. In this trial, participants were allowed to take their own allergic rhinitis relief medication, as long as they recorded the usage in the CRFs. This was both an ethical considerations as well as recognition of the likely situation in the ‘real world’. In fact, there are many different types of allergy control medications including natural products available in the market. The large variety of medications used by participants made the analysis difficult. Therefore, the medication score was clustered as “all allergic rhinitis medication score” and “antihistamine medication score” for the data analysis (see Table 40). This approach is likely to have reduced the sensitivity of the measurements. No significant difference between two groups was observed. This result is consistent with previous studies of acupuncture for allergic rhinitis (Ng et al., 2004; Xue et al., 2007).
8.3.2.5 Efficacy and participants’ expectation

As discussed in 8.3.5, the participants in the sham ear-acupressure group had a higher expectation of symptoms improvement (6.042±1.693) than those in the real ear-acupressure group (5.345±1.737) (p= 0.03) at the baseline. In contrast, the real treatment effects were in favour of the real ear-acupressure group. This supports the explanation that the treatment effectiveness was not caused by participants’ expectation.

8.3.3 Safety

Consistent with Pilot study I and Pilot study II, the main trial also demonstrated that ear-acupressure was safe for the clinical management of AR. The adverse events reported in this study were all mild or moderate discomforts, and they were liable to be tolerated or be managed by refining the pressing technique. Unlike acupuncture, there is no skin penetration involved in the acupressure method. Therefore, those adverse events which are often reported in acupuncture trials did not occur in this study. In addition, ear-acupressure is a semi-self-administered treatment. After the practitioner attached the pellets on the acupoints, the participants themselves were involved in applying pressure to the ear points by pressing the pellets three times a day. Therefore the strength and intensity of the pressure were controlled by the participants instead of by practitioner, which may have reduced the possibility of discomfort.

As discussed in Chapter 4 (section 4.2), the previous RCTs (Gao, Zhang, Zhu, & Zhang, 2008; Huo, 2003; Kong, Ren, & Lu, 2006; Qi & Wang, 2008; Rao & Han, 2006; Wang, 2004; Ye, Luo, & Xia, 2008) of ear-acupuncture/ear-acupressure for AR did not provide any relevant information about adverse events or reported that no
adverse events occurred. This is possibly because in those RCTs conducted in China, only severe adverse events were considered worthy of report. For example, the “sore feeling” was considered a normal reaction to acupuncture or acupressure ("De Qi" sensation). In contrast, in the main trial, participants were told to report any discomfort they believed was related to the treatment. Thus, all the mild and moderate discomforts were reported. Nobody reported any severe uncomfortable feeling throughout the whole trial period. All the reported adverse events were successfully managed in the first two weeks and no one withdrew from the trial due to the adverse events. Therefore, although there were some adverse events reported, this treatment is still considered as safe and well-tolerated.

8.3.4 Implications for clinical practice

Ear-acupressure is a semi-self-administered treatment. The practitioner is the person who applies pellets to certain ear acupoints while the participants themselves are the people who press the pellets three times daily during a whole week. During the eight-week treatment period, participants only needed to visit the trial clinic once a week and it only took approximately 5 minutes to attach the pellets to the ear points during each visit. Therefore, this treatment is considered to be less time consuming compared with other physical interventions such as acupuncture, which often requires treatment twice a week and takes 20 to 30 minutes each treatment session. On the other hand, being a semi-self-administered treatment, the strength and duration of points stimulation are controlled by participants, instead of practitioners. If any unbearable uncomfortable feeling occurs, participants can easily take off the pellets by themselves without attending the clinic. This makes the ear-acupressure treatment more flexible compared with other therapies.
8.4 Conclusion and recommendations

In clinical research, it is important to note that the present trial is the first randomised, sham controlled trial in the area of ear-acupressure for AR that followed a rigorous methodology. Therefore the findings from this study contribute to the body of knowledge in ear-acupressure practice by providing scientific evidence. It is suggested that the ear-acupressure protocol used in the main trial can be applied as a CAM method in clinical management of AR or as an adjunct to routine pharmacotherapy.

This trial achieved some significant results in improving symptom severity and quality of life, but did not significantly reduce medication usage. It is recommended that further studies should incorporate a more defined medication use strategy.
Chapter 9: General Discussion and Conclusion

This Chapter discusses the strengths and limitations related to the entire project on ear-acupressure for AR. In addition, recommendations are provided for further studies.

This project investigated the efficacy and safety of ear-acupressure for the management of AR, by

- systematically reviewing the current state of the clinical trial evidence from the English and Chinese literature on ear-acupuncture/ear-acupressure for AR; and
- rigorously designing and methodically conducting a series of RCTs to address the methodological flaws identified in the systematic review to determine the short- and long-term efficacy and safety of ear-acupressure for AR.

9.1 Main achievements

The entire project contains five parts: two systematic reviews, two pilot studies and the main trial.

Systematic review 1: Effectiveness and safety of ear-acupressure for AR

This review of previous ear-acupuncture/ear-acupressure RCTs for AR was published in an international peer reviewed journal (Zhang et al., 2010). The findings of this systematic review suggested that although some RCTs presented positive results for the efficacy and safety of ear-acupuncture/ear-acupressure for AR, some major methodological weaknesses existed in those studies including:

- Sham control was not included;
Quality of life assessment was not used;
Clinical effectiveness was measured as a total effective rate;
Validated outcome measure were not used;
Adverse events were not mentioned; and
Intention-to-treat method was not used.
Therefore, the findings from these RCTs could not be considered reliable due to the low methodological quality. Therefore a more rigorously designed RCT of ear-acupressure for AR was required.

Systematic review 2: Ear-acupuncture/ear-acupressure sham control methods
In order to design a single-blinded, sham-controlled RCT on ear-acupressure for AR, a systematic review of all previous RCTs of ear-acupuncture/ear-acupressure was conducted to summarise and examine the sham/placebo control methods used. Based on the findings of this systematic review, the current trial employed the “non-specific ear points” method for the sham control.

Pilot study I: Ear-acupressure for AR RCT (feasibility study)
Once the trial protocol was finalised, a pilot study was conducted between May and November 2008 to examine the feasibility of the protocol. According to feedback from this pilot study, a few minor changes were made to the original protocol. This was a critical step toward conducting the second pilot study and the main trial.

Pilot study II: Ear-acupressure for AR RCT (efficacy study)
The second pilot study was conducted between September and December 2008 in order to provide data for sample size estimation for the main trial. Sixty-three SAR participants were included in this pilot study, the results of which were published in a
peer reviewed journal (Xue et al., 2011) (Appendix A4.3). Based on the results of this study, it was estimated that the main trial required 116 participants in each group and 232 in total.

**The main trial: Ear-acupressure for AR RCT**

The ear-acupressure for AR main trial was an adequately powered, international, multi-centre, single-blinded, RCT. This PhD project was to investigate the efficacy and safety of ear-acupressure for allergic rhinitis at the Australia centre of the multi-centre trial. Therefore, only the results from the Australian trial centre were reported in this thesis. The main trial at the Australia centre was conducted in the years of 2009 and 2010. The trial recruiting and treatment period was scheduled in non-pollen season (between April and September); the follow-up period was ended at spring season (November). A total of 117 PAR participants were included in the trial. This main trial demonstrated that ear-acupressure was effective in relieving AR symptoms and improving participants’ quality of life. Short-term effectiveness was shown in: total nasal symptoms, sneezing, blocked nose, itchy nose, watery eyes, global nasal and non-nasal symptoms, global quality of life, activity and sleep; while long-term effectiveness was found for: total nasal symptoms, blocked nose and sleep. No severe adverse event was reported during the treatment and follow-up periods. Ear-acupressure was also proven to be safe and well-tolerated for AR participants. However, ear-acupressure did not reduce participants’ relief medication usage.

It is suggested that ear-acupressure is an effective and safe CAM method in clinical management of AR.
9.2 Strengths and limitations

9.2.1 Strengths of the study

This entire study was conducted following the flow of: systematic review 1 → systematic review 2 → Pilot study I → Pilot study II → main trial. This was a logical and consistent approach that firstly investigated the state of the current evidence, identified weakness in the existing trials and sought to refine the trial methodology before moving to the main trial.

9.2.1.1 Systematic reviews prior to the RCT

Two systematic reviews were conducted in 2008 before the development of the trial protocol. These two reviews provided the fundamentals of the clinical trial. Without them, the appropriate methodology including the important aspects of point selection and sham control method could not have been established.

9.2.1.2 RCTs of ear-acupressure for AR

Upon the finalisation and approval of the trial protocol, instead of commencing the main trial immediately, two pilot studies were conducted to test the feasibility and collect data for sample size estimation. As a result of the data and expertise gained in the pilot studies, it was possible to undertake the main trial as an international collaborative, multi-centre study to investigate the efficacy and safety of ear-acupressure for AR.

This trial assessed not only the short-term efficacy and safety (at the end of the eight weeks treatment period) but also the long-term efficacy and safety by including a 12-week follow-up period.
Furthermore, three developed and commonly used questionnaires were used in this trial to evaluate the AR symptom severity and quality of life, they are:

- Juniper 4 point symptom severity scale (Juniper et al., 2005)
- Spector 7 point VAS (Spector et al., 2003)
- RQLQ(S) (Juniper, Thompson, Ferrie, & Roberts, 1999)

RQLQ(S) was used instead of RQLQ, following the suggestion from the originator of this questionnaire, in order to increase the consistency and reliability of the results of questions about activities.

With regard to the statistics, intention-to-treat analysis was employed in this trial for missing data to reduce bias. Given the fact that the AR symptoms may be relieved spontaneously along with the weather/environment change, all missing data was replaced using the conservative worst-case-scenario method.

These aspects ensured the development of an appropriate methodology for this clinical trial. The results indicate that the rigorous design was also rigorously conducted, so the findings from the current trial are reliable, and the conclusions that ear-acupressure may be effective and safe for AR management are warranted.

9.2.2 Limitations of the study

9.2.2.1 Systematic reviews prior to the RCT

Firstly, only English and Chinese language databases were searched due to language barriers, so some relevant studies published in other languages such as Korean and German may have been missed. This might have an impact on our conclusions. Secondly, these two systematic reviews were conducted in 2008 prior to designing the trial protocol and followed the Cochrane Handbook for Systematic
Reviews of Interventions 4.2.6 (Higgins & Green, 2006). However, there have been some amendments to the review methodology in the latest version of the Cochrane Handbook (Cochrane Handbook for Systematic Reviews of Interventions 5.1.0) (Higgins & Green, 2011). For instance, a PRISMA flow diagram is employed in the “Results of the search” section. The Jadad scale is no longer used for study methodological quality assessment. Instead, risk of bias assessment is employed.

9.2.2.2 RCTs of ear-acupressure for AR

There are some limitations of the RCTs, as follows:

- The pellets used in the trial could not always be kept attached to the ear points throughout the whole treatment week. The pellets on the real points (such as Internal Nose (TG₄) and Adrenal Gland (TG₂₉)) are more likely to be detached compared with those on the points used for the sham group due to the different locations.

- Cost-effectiveness analysis was not performed in the current RCT. Firstly, instruments suitable for QALY calculation were not used. For example, SF-36 was not employed as an outcome measure. SF-36 is a survey of patients’ general health. It is commonly used in health economics as a variable in the QALY calculation to determine the cost-effectiveness of a health intervention.

- The symptom relief medication was not standardised. Participants were permitted to use their preferred symptom relief medication if needed. Although the medication usage data were categorised as antihistamines and others for the data analysis, due to the large variety of medications used by the trial participants, it was difficult to identify the medication type in the “others” category. This made it impossible to perform correlation analysis between cost and effectiveness. It is also possible that participants who use a preferred
relief medication tend to maintain use habitually even when symptoms are mild. By providing a different relief medication at the beginning of the trial, any such effect could be controlled for.

The above mentioned limitations should be considered in future studies.

9.3 Implications for future studies

Based on the findings of the systematic reviews and the RCTs, it is suggested that further studies be conducted to address the following aspects.

9.3.1 Cost-effectiveness of ear-acupressure

As discussed in Chapter 2 (section 2.7), AR causes a significant impact on patients’ quality of life and is an economic burden that includes both the direct costs of health care and the indirect costs caused by patients’ incapacity for work. Therefore it is important to investigate the cost-effectiveness of an AR therapy rather than the efficacy and safety only. For example, a recent large sized study concluded that using acupuncture in addition to routine care to treat patients with AR was cost-effective (Witt, Reinhold, Jena, Brinkhaus, & Willich, 2009). As a subtype of acupuncture, ear-acupressure is a kind of semi-self-administered technique. It requires less frequent clinic visits and shorter treatment duration than acupuncture. Thus, a separate cost-effectiveness evaluation is needed. The results may help with policy makers’ decision-making. It is recommended that further studies should include the SF-36 survey for QALY calculation.

In addition, participants should be issued with a standard relief medication during the trial and given instructions for its use to ensure the relief medication data is more
accurate and avoid the bias due to unclear medication scoring. In accordance with
this arrangement, correlation analysis between cost and effects is possible.

9.3.2 Investigation of the mechanism

The underlying mechanism of ear-acupressure requires investigation.

Firstly, whether the effectiveness of ear-acupressure treatment was induced by the
combination of the five points or was due only to specific points needs to be further
assessed. Future studies may consider isolating the five ear points into subgroups
and investigating the specific point function.

Secondly, similar to acupuncture for the management of AR, the physiological
mechanisms of ear-acupressure’s action on AR are yet to be elucidated. In recent
years, a number of animal experiments and clinical trials have been conducted to
investigate the anti-inflammatory effects of acupuncture (section 3.4.4). Being similar
to acupuncture, ear-acupuncture/ear-acupressure may produce similar effects by
means of similar pathways. For example, a study tested both ear-electroacupuncture
and body electroacupuncture concluded that these two approaches both can
effectively relieve endometriosis-induced dysmenorrhea, which may be closely
related to their effects in reducing plasma PGE2 and increasing 6-Keto-PGF1alpha
level (Jin, Sun, & Jin, H. F. 2009). Another study compared body acupuncture and
ear-acupuncture for anxiety and concluded that both ear-acupuncture and body
acupuncture treatment methods were effective in decreasing anxiety in preoperative
patients (Wu, Liang, Zhu, Liu, & Miao 2011). However, the exact mechanism of ear-
acupuncture/ear-acupressure remains unclear. A RCT on ear-acupuncture for
migraine suggested that the therapeutic specificity of auricular points exists and is
linked to the somatotopic representation of our body on the ear (Allais et al., 2011). When treating AR, an RCT demonstrated that ear-acupressure and body acupuncture had similar symptomatic relief effects and caused similar changes in cytokines (IL-4) and serum total IgE level in AR participants (Rao & Han, 2006).

Further well-designed studies on ear-acupressure for AR will be needed to confirm any anti-inflammatory effects of ear-acupressure.

9.4 Implications for clinical practice

As discussed in Chapter 8 (section 8.3.4), ear-acupressure is a semi-self-administered treatment. It is considered to be a less time-consuming and safer approach compared with the traditional acupuncture technique. Once the cost-effectiveness of this therapy is established, it is anticipated that practitioners should consider this treatment once a week for at least eight weeks for AR management. Practitioners should give patients clear instructions with regard to the proper way of pressing pellets and maintaining their adhesion.
References


Australasian Society of Clinical Immunology and Allergy (ASCIA). (2007). The economic impact of allergic disease in Australia: not to be sneezed at.


Appendices

Appendix one: Instruments for trial recruitment

A1.1 Advertising Poster

---

Do you suffer from Hay Fever?
Do you have symptoms such as sneezing, blocked nose, running nose or itchy nose?
Are you interested in participating in a research project:

**Ear- acupressure for Hay Fever**

Ear-acupressure is a non-invasive technique that does not involve needles.

A few tiny pellets are attached to your ear with an adhesive tape weekly.

All you need to do is to press the pellets a few times a day.

Preliminary studies have demonstrated that this painless technique is effective in treating several medical conditions including hay fever.

This research project is designed to scientifically determine if this simple technique is useful to relieve the symptoms of hay fever.

If you meet the inclusion criteria and agree to participate, you may receive ear-acupressure treatment once a week for eight weeks by a registered acupuncturist.

The research will be undertaken at the Chinese Medicine Clinical Trial Laboratory:
RMIT Bundoora West Campus and RMIT City Campus in Melbourne.

For further details of participation please contact:
Ms Claire Shuiqing Zhang, PhD researcher
Registered Chinese Medicine and Acupuncture Practitioner
Tel: 03 99257002 or 0402103088
Email: s.zhang@student.rmit.edu.au
A1.2 Plain Language Statement

School of Health Sciences, Chinese Medicine Research Group

PLAIN LANGUAGE STATEMENT (PLS)

PROJECT TITLE: Ear-acupressure for Hay Fever

Dear Participant,

My name is Claire Shuiqing Zhang. I am a PhD candidate at the Division of Chinese Medicine, School of Health Sciences, RMIT University and am supervised by Prof Charlie Xue, Dr Angela Yang, A/Prof Frank Thien, Dr George Lenon and A/Prof Cliff Da Costa. This letter is to invite you to participate in our research project – a randomised controlled clinical trial for hay fever. This information sheet describes the project in detail. Please read this sheet carefully and be sure that you understand its contents.

If you decide to take part in this study after you have carefully read the information in this Plain Language Statement, please complete the TWO (2) enclosed questionnaires (Attachment 2-3: General Information Questionnaire; and Attachment 2-4: Screening Questionnaire) in this general information pack, and send the two completed questionnaires to the research team in the prepaid envelop provided. If you and your condition are suitable, according to the inclusion criteria for this study, I will contact you by phone to organise an appointment at either the RMIT Bundoora campus or the RMIT City campus for an assessment interview. If you do not meet the inclusion criteria, I will inform you by sending you a letter within two weeks of receiving your returned forms. During the assessment interview, you may ask any questions you may have concerning this study to help you make the final decision to participate.

1. Purpose and background of this research
The prevalence of hay fever has increased worldwide in the last decades. Ear-acupressure is a non-invasive method using pellets to press the points on the ears to achieve therapeutic effects. It has been used for hay fever management for many years. The Division of Chinese Medicine at RMIT University has extensive experience in research into hay fever, and we now would like to further investigate scientifically whether ear-acupressure reduces the severity and frequency of hay fever symptoms, decreases the usage of medications as well as improves the quality of life for the participants with hay fever. To do this we will conduct a randomised, single-blind, sham-controlled clinical trial. This means that one group will receive the real ear-acupressure treatment and the other group, the control, will receive a treatment that appears the same but is not the true treatment (i.e. sham treatment). Neither the experimenters nor the participants will know which group is which until the end of the clinical trial. The results of this research project may lead to a cost-effective, alternative option for the treatment of hay fever.

This project has been reviewed and approved by the Human Research Ethics Committee of RMIT University. It is covered by RMIT University, Broadform Public and Product Liability Insurance.
2. What you have to do if you participate

If you would like to participate in this research project, you must be between 18 and 70 years of age and have had hay fever for more than two years. You will not be able to participate if you are currently under systemic corticosteroid therapy or have a current active respiratory disease such as asthma. We will need to know your medical history in relation to allergies, respiratory diseases and other conditions relevant to hay fever.

This is a randomised, single blind, sham controlled clinical trial. You will be joining more than 200 other hay fever sufferers. You will have 50% chance of being randomly assigned to either the active ear-acupressure group or the control ear-acupressure group. This design allows us to compare the therapeutic effects of the active treatment with the control treatment. If the results of this study show that ear-acupressure is effective in the treatment of hay fever, then we will be happy to provide free active ear-acupressure treatment at the completion of the study to those who were in the control group.

Your participation will involve an initial interview, a two-week run-in period, an eight-week treatment (real or sham) period and a twelve-week follow-up period. In total your involvement in this research project will continue for 22 weeks but you will only need to come to RMIT on nine occasions.

During the initial assessment interview, you will be asked to attend the Clinical Trial Laboratory once. At this time you will sign an informed consent form, complete an assessment questionnaire, undertake an allergy test (skin prick test) and have a nasal examination.

During the eight-week treatment period, you will be asked to attend the Clinical Trial Laboratory once a week for ear-acupressure treatment. The ear-acupressure will be done using commercially available stainless steel press-pellet tapes. The press-pellet measures 1 mm in diameter and is attached to a round adhesive tape in a tan colour which is close to skin colour and measures 5 mm in diameter. During the treatment, you will be seated comfortably in an armchair and the practitioner will tape the pellets on the real or sham ear points on one of your ears. Once taped, the practitioner will show you how to press each pellet to achieve the therapeutic effects. There is no skin penetration in the treatment. In the subsequent treatment session, the other ear will be used for taping. Thus, the two ears will be used alternately on a weekly basis.

You will be asked to press the five pellets three times a day once they have been taped on your ear. The practitioner will show you how to do this. The pressing technique is to promote the desired stimulation on the points used for hay fever. Over the week, some pellets may become unstuck and fall off.

You will also be asked to:

- record your medication usage using the diary form provided;
- record the medical expenses related to your hay fever (ie. medical practitioner visits, diagnostic testing, purchase of home aids and services);
• complete the fortnightly assessment forms,
• record how many press-pellets remain stuck to your ear per day using the diary form provided,
• record your opinions about the ear-acupressure at the end of week 1 and the end of week 8, and record any adverse events you experience relating to ear-acupressure.

These forms are designed to be easy to fill in and should not require much of your time.

You should stay at the same address or in the same suburb for the whole 22 week since hay fever is affected by the environment and the allergens can be different in different areas. Such changes can influence the results of the research project.

3. Potential risks of ear-acupressure treatment
All the ear points to be used in this research project have been used in previous clinical studies and no adverse events have been reported. Generally, pain or discomfort associated with ear-acupressure is very minor. However, some individuals may experience some minor pain after prolonged pressing. Others may find the surface of their skin becomes temporarily sticky after the pellets are removed from the ear. If any unforeseen event occurs, please record it on the form provided and report it to the investigators as soon as possible.

4. Skin prick test
During the initial interview, you will be asked to have a Skin Prick Test. This test is to find out which allergen(s) cause your allergic reactions. A trained practitioner will perform the test following the standard procedure used in everyday practice. In order to obtain an accurate outcome of the Skin Prick Test it is preferable that you do not take oral medications for hay fever three (3) days prior to the test. Except for the three days prior to the skin prick test, you are expected to continue to take your medication as needed, and record the medication taken on the diary form.

5. Physical Examination
This involves physical examination of the nose during the initial interview. It will be carried out by a qualified medical practitioner. The examination includes a visual inspection of the anatomical position of the septal cartilage, the appearance of the mucosa of the nasal cavities, the physical nature and colour of the nasal turbinates, inspection of nasal secretions, and an assessment of the flow of air through the nasal passages.

6. Confidentiality of information you provide
All information provided by you and the data collected through this research project will be stored in a password protected computer program. All files will be kept securely in a locked filling cabinet at RMIT and will be retained for 15 years and then will be shredded and disposed of as required by the Therapeutic Goods Administration (TGA). Your records may be inspected by authorised persons for the purpose of an original data audit. In all publications, all your personal information will be removed so your identity will not be revealed. You have the right to access your personal data at a time prearranged with the investigators.
7. **Your rights as a participant**

Participation in this project is voluntary. You may discontinue your participation at any time. You may ask the investigators any questions concerning the project at any time. Please contact me, Claire Shuiqing Zhang, on 9925 7002 or 0402103088 when you have any questions about this project.

Yours sincerely,

Claire Shuiqing Zhang,
PhD Candidate
The RMIT Chinese Medicine Research Group

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. The telephone number is (03) 9925 2251.

Details of the complaints procedure are available from the above address.
A1.3 Informed Consent Forms

Prescribed Consent Form for Persons Participating In Research Projects Involving Tests and/or Medical Procedures

Portfolio
School of
Name of participant:

Science, Engineering and Technology Portfolio
Health Sciences

Project Title: Ear-acupressure for allergic rhinitis

Name(s) of investigators:

(1) Shuiqing Zhang Phone: 03 9925 7002
(2) Charlie Xue Phone: 03 9925 7745
(3) Angela Yang Phone: 03 9925 7175
(4) George Lenon Phone: 03 9925 6587
(5) Clifford Da Costa Phone: 03 9925 6114

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 all the participants. Any information which will identify me will not be used.

Participant’s Consent

Participant: ___________________________ Date: ___________________________

(Signature)

Witness: ___________________________ Date: ___________________________

(Signature)

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. The telephone number is (03) 9925 2251. Details of the complaints procedure are available from the above address.
Prescribed Consent Form For Persons Participating In Research Projects Involving Interviews, Questionnaires or Disclosure of Personal Information

Portfolio
School of
Name of participant:

Project Title:

Science, Engineering and Technology Portfolio
Health Sciences

Ear-acupressure for allergic rhinitis

Name(s) of investigators:  
(1) Shuiqing Zhang  
Phone: 03 9925 7002
(2) Charlie Xue  
Phone: 03 9925 7745
(3) Weihong Yang  
Phone: 03 9925 7175
(4) George Lenon  
Phone: 03 9925 6587
(5) Clifford Da Costa  
Phone: 03 9925 6114

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 all the participants. Any information which will identify me will not be used.

Participant’s Consent

Participant: ___________________________ Date: ________________
(Signature)

Witness: ___________________________ Date: ________________
(Signature)

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. The telephone number is (03) 9925 2251.
Details of the complaints procedure are available from the above address.
A1.4 General Information Questionnaire

School of Health Sciences, Chinese Medicine Research Group
GENERAL INFORMATION QUESTIONNAIRE
(To be completed by participant and returned to the research team in the pre-paid envelope)

PLEASE WRITE CLEARLY TO HELP US MAINTAIN ACCURATE RECORDS

1. Family Name: ___________________________  First Name: ___________________________
2. Date of Birth: ___________________________  /  /  Gender: Male  Female
3. Address: ________________________________
   Post code: ______________________________
   Email: _________________________________
   Mobil: ________________________________
   Best time to call you: ___________________
5. Emergency contact:
   Name: _________________________________
   Address: ______________________________
   Post code: _____________________________
   Telephone No:  Home  Work  Mobile
6. Currently married/partnered?  Yes  No
7. Occupation: (Current) ______________________________
8. Education completed  Primary school ______________________________
   High / Secondary School ______________________________
   TAFE / Technical college ______________________________
   University degree ______________________________
10. Please list the regular medicine you use for Hay Fever and/or other drugs you take for other diseases/symptoms.

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Medical condition</th>
<th>Dosage</th>
<th>Frequency (times/day or week)</th>
<th>How long have you been taking it?</th>
</tr>
</thead>
<tbody>
<tr>
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</table>
A1.5 Screening Questionnaire

School of Health Sciences, Chinese Medicine Research Group
SCREENING QUESTIONNAIRE
(To be completed by participant and returned to the research team in the pre-paid envelope)
PLEAS WRITE CLEARLY TO HELP US TO MAINTAIN ACCURATE RECORDS

Name: ______________________ Date: __/__/__
DOB: __/__/__ Gender: Male Female

Section I:
1. Compared to 2007, my hay fever in 2008 was:
   +2 Much less severe
   +1 Less severe
   0 Same severity
   -1 Moderately worse
   -2 Very much worse

2. Compared to 2006, my hay fever in 2007 was:
   +2 Much less severe
   +1 Less severe
   0 Same severity
   -1 Moderately worse
   -2 Very much worse

3. Compared to 2005, my hay fever in 2006 was:
   +2 Much less severe
   +1 Less severe
   0 Same severity
   -1 Moderately worse
   -2 Very much worse

Do any of your family members suffer from any kind of allergic disease such as
perennial allergic rhinitis or seasonal allergic rhinitis (hay fever), asthma, etc? If yes,
please specify by ticking the appropriate box:

<table>
<thead>
<tr>
<th>Family Member</th>
<th>Not affected</th>
<th>Hay fever</th>
<th>Asthma</th>
<th>Eczema</th>
<th>Others (Please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brother 1</td>
<td></td>
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<tr>
<td>Brother 2</td>
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<tr>
<td>Brother 3</td>
<td></td>
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<tr>
<td>Sister 1</td>
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<tr>
<td>Sister 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sister 3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Which allergic diseases do you suffer from?
   - Hay fever
   - Asthma
   - Eczema/Dermatitis
   Others (please specify):

5. At what age did your allergy occur for the first time?
   - Hay fever: Age
   - Asthma: Age
   - Eczema/Dermatitis: Age
   Others (please specify):

6. Your opinion of the cause of your hay fever

7. Your hay fever symptoms are worse when:
   - Outdoors
   - At home
   - At night
   - During the day
   - On waking
   Others (please specify):

8. Do your hay fever symptoms occur in certain months or over the whole year?
   - In certain months
   - Whole year

If your hay fever symptoms occur in certain months:
   (1). in which month(s) do your symptoms occur each year, and
   (2). which are the worst months? (Please circle the months)

<table>
<thead>
<tr>
<th>(1). Occur in months</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
<th>Jul</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>(2). Worse in months</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
<th>Jul</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
</tr>
</thead>
</table>

11. Does the severity of your hay fever symptoms relate to the environment? If yes, please specify.
   - Yes:
     - Garden
     - Pollution
     - Outdoors
     - Cats
     - At home
     - Dogs
     - Windy days
     - Smoke
     Others (specify):

   - No

12. Age of your house: ________________ years
    Period of residence: ________________ months/years
13. Bedroom environment
Pillow:  Age  Filling type
Mattress: Age  Filling type
Type of bed cover:  Quilt/ Doona/ Eiderdown  Blankets

14. Material used to make/fill bed cover:
Feathers  Wool  Cotton  Synthetic

15. Do you have carpet in your house? If yes, what kind of material is it made of?
   Yes:  Wool  Synthetic  Cotton
   No

16. Which of the following animals do you have regular contact with?
   Dog  Cat  Horse  Rabbit  Sheep  Cow
   Others (specify)
   Please estimate frequency and length of exposure

17. Are there any foods that you avoid (please list):
   Why?

18. Do your hay fever symptoms occur for:
   Less than 4 days per week
   More than 4 days per week

19. Do your hay fever symptoms occur for:
   Less than 4 consecutive weeks
   More than 4 consecutive weeks

20. What is the severity of your current hay fever nasal symptoms, on a 4 point scale?
   (Please circle one number for each symptom to indicate its severity)

<table>
<thead>
<tr>
<th>Hay Fever Symptom</th>
<th>Severity of Symptom (please circle one number for each symptom)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0</td>
</tr>
<tr>
<td>Stuffy / blocked nose</td>
<td>0</td>
</tr>
<tr>
<td>Runny nose</td>
<td>0</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>0</td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>0</td>
</tr>
<tr>
<td>Watery eyes</td>
<td>0</td>
</tr>
<tr>
<td>Redness of eyes</td>
<td>0</td>
</tr>
<tr>
<td>Itchiness of ears and/or throat/palate</td>
<td>0</td>
</tr>
</tbody>
</table>
21. What is the severity of your current hay fever symptoms on a 7 point scale? (Please circle one number for each symptom to indicate its severity)

<table>
<thead>
<tr>
<th>Hay Fever Symptom</th>
<th>Severity of Symptom (see below)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sneezing</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Runny nose</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Congestion (stuffiness)</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Postnasal drip</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Throat symptoms</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Ear symptoms</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Headache</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Mental function</td>
<td>1 2 3 4 5 6 7</td>
</tr>
</tbody>
</table>

*1 = None- to an occasional limited episode;
2 = Between 1 and 3;
3 = Mild- Steady symptoms but easily tolerable;
4 = Between 3 and 5;
5 = Moderately Bothersome- Symptoms hard to tolerate, may interfere with activities of daily living and/or sleep;
6 = Between 5 and 7;
7 = Unbearably severe- Symptoms are so bad, person can’t function all the time.

22. What is the global assessment of nasal and non-nasal symptoms severity?
Score = _______ (from 1 to 7)

N.B. Please note this particular question assesses your combined nasal and non-nasal symptoms. Also, the scale is the reverse of the previous assessment scales: So 1 means unbearably severe; and 7 means no symptoms*. See below:

*Key to symptoms:
1 = Unbearably severe- Symptoms are so bad, person can’t function all the time
2 = Between 1 and 3
3 = Moderately Bothersome- Symptoms hard to tolerate, may interfere with activities of daily living and/or sleep
4 = Between 3 and 5
5 = Mild- Steady symptoms but easily tolerable
6 = Between 5 and 7
7 = None- to an occasional limited episode
23. What treatment can ease your hay fever symptoms?
   Please specify the name of any medications you find effective:

   Please specify any other treatments you find effective for your hay fever symptoms:

24. Have you been taking long acting antihistamines (such as Astemizole, Cetirizine, Loratadine) within the last three months?
   Yes
   Please specify
   When did you last take them

   No

25. Have you been treated by oral cortisone/steroid tablets/cortisone injections within the last three years for hay fever or other conditions?
   Yes
   Please specify
   When

   No

26. Did you have Immunotherapy within the last three years for your hay fever?
   Yes
   Please specify
   When

   No

27. Have you changed your regular medication for hay fever in the last three months?
   Yes
   Please specify
   When

   No

28. Have you ever been diagnosed with nasal polyps?
   Yes
   In which year

   No

29. Do you have any other respiratory diseases?
   Yes
   TB
   Asthma
   Bronchiectasis
   Others, specify

   No
30. Do you have any other diseases including infectious diseases?
   Yes       Please specify
   No

31. If you are female, are you currently pregnant?
   Yes       Please specify how many months
   No

32. What is your smoking status?
   Current
   Former
   Never
   If current, how many cigarettes per day and for how many years?
   per       years
   _____     _____

33. Are you wearing hearing aid?
   Yes
   No

34. Have you been treated by ear-acupressure? If yes, for what condition?
   Yes       When
   No       Please specify
   Yes
   No
Section II:
Chinese medicine syndrome differential diagnosis questionnaire (please tick yes or no in the box):

<table>
<thead>
<tr>
<th>Differentiation of Hay Fever Syndrome</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 Is your nose blocked?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2 Do you have an itchy nose?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3 Do you sneeze a lot?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A4 Do you have a running nose?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5 Is your sense of smell reduced?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A6 Do you catch cold easily or is it difficult for you to recover from colds?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A7 Do you sweat easily, even when you are not doing exercise?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A8 Do you often cough?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1 Do you get headaches or feel heavy headed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2 Do you feel tired or exhausted?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3 Do your limbs feel heavy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B4 Do you lose your appetite?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B5 Do you often have loose bowels?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B6 Do you feel full in the stomach even when you haven’t just eaten?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1 Are you sensitive to the cold?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2 Do your limbs feel cold?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3 Do you feel weak, especially in the lumbar area, or the knees?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4 Do you usually get up in the night to pass urine frequently?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C5 Do you get short of breath easily after slight physical exercise?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# A1.6 Skin Prick Test

## Skin Prick Test Result

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date:</th>
<th>Time:</th>
<th>Gender:</th>
<th>SPT Result</th>
<th>Allergen</th>
<th>Diameter of wheal (mm)</th>
<th><strong>POSITIVE</strong> (If diameter is greater than negative control by 3mm or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Positive</td>
<td>1 Negative Control: Saline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female</td>
<td>Negative</td>
<td>2 Grass Mix #7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>3 Perennial Rye</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>4 Ragweed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>5 Mould Mix #10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>6 Cat Hair</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>7 Dog Hair</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>8 Dust Mite</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>9 Positive Control: Histamine (10mg/ml)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Recorder**

name: ___________________________ Date: __________ / _______ / _______
A1.7 Physical Examination

1. **Main Complaint:***

2. **Current Medical History:***

3. **Patient Medication for allergic rhinitis:**
   - ☐ H1-antihistamines
   - ☐ Chromones
   - ☐ Antibiotics
   - ☐ Corticosteroids (systemetic)
   - ☐ Anticholinergics
   - ☐ Anti-leukotrienes
   - ☐ Nasal Corticosteriod sprays
   Specify the name of the drug ________________________________

4. **Past Medical History**
   - ☐ HIV
   - ☐ Hepatitis
   - ☐ Heart Disease
   - ☐ Renal Disease
   - ☐ High Blood Pressure

5. **Allergens:**
   - ☐ Pollen
   - ☐ Animals
   - ☐ Food
   - ☐ Fruit
   - ☐ Drugs
   - ☐ Chemicals (industrial or cosmetic)
   - ☐ Others

6. **Blood Pressure:**
   - Diastolic BP __________________ mmHg
   - Systolic BP __________________ mmHg

7. **Heart Rate** __________________
8. Physical Examination of Nose:

- Septal Cartilage
  - Normal midline anatomic position
  - Abnormal anatomic position (Deviated)
  - Deviated to left
  - Deviated to right
  - Deviated to both sides

- Nasal Cavities Mucosal Appearance
  - Normal nasal mucosa
  - Pale nasal mucosa
  - Hypaemic nasal mucosa
  - Dehydrated nasal mucosa (dry nasal mucosa)
  - Hypertrophied nasal mucosa
  - Others

- Nasal turbinates
  - Normal superior, middle and inferior turbinates
  - Hypertrophied turbinates
  - Atrophic turbinates
  - Swollen turbinates
  - Others

- Nasal turbinates colour
  - Normal pink mucosal colour
  - Abnormal mucosal colour
  - Pale colour
  - Purplish, congested colour
  - Hyperaemic colour
  - Others

- Nasal secretion
  - Normal thin mucoid nasal secretion
  - Abnormal nasal secretion
  - Watery discharge:
    - Serous
    - Seromucinous
  - Purulent discharge:
    - Yellow
    - Green
    - Yellow Green
    - Mucopurulent discharge
    - Post nasal discharge

- Patient’s Nasal Pathway Situation
  - Patient breathes easily via nose
  - Patient cannot easily breathe via nose
  - Patient feels total nasal block
  - Others

- Patient’s other associated clinical symptoms
  - Disturbed sleep
  - Pharyngitis
  - Tonsillitis
  - Snoring
  - Smelling function disorders
  - Others
Clinical Diagnosis:_____________________________________________________

Recorder name:_________________________________Date:_____/_____/_____
### A1.8 Chinese Medicine Syndrome Differential Diagnosis Questionnaire

**School of Health Sciences**  
Chinese Medicine Research Group

#### CHINESE MEDICINE SYNDROME DIFFERENTIAL DIAGNOSIS QUESTIONNAIRE

<table>
<thead>
<tr>
<th>Differentiation of AR Syndrome</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) Lung deficiency</strong> due to external wind-cold pathogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Is your nose blocked? (A); (B); (C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you have itchy nose? (A); (B); (C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you sneeze a lot? (A); (B); (C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you have running nose? Is the nasal discharge (A) clear? Or (B) &amp; (C) white in colour?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Is your sense of smell reduced? (A) &amp; (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you catch cold easily or is it difficult for you to recover from cold?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you sweat easily, even when you are not doing exercise?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you often cough?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(B) Spleen deficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Do you have headache or heavy headed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you feel tired or exhausted?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do your limbs feel heavy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you lose your appetite?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Do you often have loose bowels?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you feel full in the stomach even when you haven’t just eaten?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(C) Kidney Yang deficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Are you sensitive to the cold?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do your limbs feel cold?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you feel weak, especially in the lumbar area, or the knees?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you usually get up in the night to pass urine frequently?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Do you get short of breath after slight physical exercise?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Tongue | (A) Pale colour; white coating  
(B) Pale colour or enlarged with teeth mark; white coating  
(C) Pale colour |
|--------|------------------------------------------------|
| Pulse | (A) Superficial & weak  
(B) Weak & thready  
(C) Deep & weak |

#### Chinese Medicine Differential Diagnosis

**Differentiation:**

<table>
<thead>
<tr>
<th>(1) Lung Deficiency</th>
<th>(3) Lung + Kidney Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) Lung + Spleen Deficiency</td>
<td>(4) Lung + Spleen + Kidney Deficiency</td>
</tr>
</tbody>
</table>
### Inclusion Criteria

(If the answer to any of these questions is **NO**, the patient is excluded.)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged between 18 and 70 (inclusive);</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With a history of <strong>at least two years</strong> of typical symptoms of allergic rhinitis;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive skin prick test to any one or more of the following allergens:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seven-grass mix, Perennial Rye, Ragweed, House mite, Animal’s dander or Mould Mix;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently not involved in other clinical trials for the treatment of allergic rhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written informed consent for participant signed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Exclusion Criteria

(If the answer to any of these questions is **YES**, the patient is excluded.)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current systemic corticosteroid therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other current active respiratory disease such as asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal polyposis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other structural defects of the upper respiratory tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wearing hearing aid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of being allergic to adhesive tape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of HIV, Hepatitis B or C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have used ear-acupressure for respiratory diseases over the last six months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not comprehend English</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Signature: ____________________________
Date: ______/_____/______
Appendix two: Case report form

A2.1 Instructions for completing CRFs

INSTRUCTIONS FOR COMPLETING CRFS

This should state the following:

- **Pen:**
  
  Always use a black ball-point pen when writing in CRFs.

- **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 the give 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.
# A2.2 Daily 4 Point Scale Symptom Assessment

## DAILY SYMPTOM SEVERITY SCORES OF ALLERGIC RHINITIS

Please assess your daily symptom severity of the hay fever from the first day of the treatment week. Score the symptom severity according to the following judgement scale and mark it in the corresponding boxes below:

**Key to symptoms:**

- 0 = no symptoms,
- 1 = mild symptoms (symptoms that are present but not particularly bothersome),
- 2 = moderate symptoms (symptoms that are bothersome but do not interfere with daily activities),
- 3 = severe symptoms (symptoms that are bothersome and interfere with daily activities or disturb sleep).

<table>
<thead>
<tr>
<th>Hay Fever Symptoms</th>
<th>Daily Symptom Severity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Sneeze</td>
<td></td>
</tr>
<tr>
<td>Stuffy / blocked nose</td>
<td></td>
</tr>
<tr>
<td>Runny nose</td>
<td></td>
</tr>
<tr>
<td>Itchy nose</td>
<td></td>
</tr>
<tr>
<td>Itchy eyes</td>
<td></td>
</tr>
<tr>
<td>Watery eyes</td>
<td></td>
</tr>
<tr>
<td>Redness of eyes</td>
<td></td>
</tr>
<tr>
<td>Itchiness of ears and/or</td>
<td></td>
</tr>
</tbody>
</table>

*References:*

A2.3 Fortnightly/Weekly 4 Point Scale Symptom Assessment

The School of Health Sciences  Chinese Medicine Research Group

WEEKLY ALLERGIC RHINITIS SYMPTOM SEVERITY ASSESSMENT

4 Point Scale Symptom Assessment

What is the overall severity of your hay fever symptoms during the last week assessed by 4 point scale? (Please circle one number of each symptom to indicate its severity) (Juniper et al., 2005)

<table>
<thead>
<tr>
<th>Hay Fever Symptoms</th>
<th>Severity of Symptoms (please circle one number for each symptom)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0</td>
</tr>
<tr>
<td>Stuffy / blocked nose</td>
<td>0</td>
</tr>
<tr>
<td>Runny nose</td>
<td>0</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>0</td>
</tr>
<tr>
<td>Itchy eyes</td>
<td>0</td>
</tr>
<tr>
<td>Watery eyes</td>
<td>0</td>
</tr>
<tr>
<td>Redness of eyes</td>
<td>0</td>
</tr>
<tr>
<td>Itchiness of ears and/or palate</td>
<td>0</td>
</tr>
</tbody>
</table>

**Key to symptoms:**

0 = no symptoms,
1 = mild symptoms (symptoms that are present but not particularly bothersome),
2 = moderate symptoms (symptoms that are bothersome but do not interfere with daily activities),
3 = severe symptoms (symptoms that are bothersome and interfere with daily activities or disturb sleep).

**References:**

### A2.4 Fortnightly/Weekly 7 Point Visual Analogue Scale (VAS)

7 Point Visual Analogue Scale (VAS)

Please indicate your response on the following visual analogue scales by circling the appropriate number following the keys given below. As an example, if your sneezing is “Mild- Steady symptoms but easily tolerable” (= 3), then answer by circling number “3” as shown below.

<table>
<thead>
<tr>
<th><strong>Sneezing</strong></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Now, please answer the following five questions by circling a number with the help of the Keys below the questions:

**Question 1.** Assessment of nasal symptom severity (during the last week).

<table>
<thead>
<tr>
<th><strong>Sneezing</strong></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Runny nose</strong></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Congestion (stuffiness)</strong></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Itchy nose</strong></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Postnasal drip</strong></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Total nasal symptoms</strong></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key to symptoms:**

1 = None- to an occasional limited episode
2 = Between 1 and 3
3 = Mild- Steady symptoms but easily tolerable
4 = Between 3 and 5
5 = Moderately Bothersome- Symptoms hard to tolerate, may interfere with activities of daily living and/or sleep
6 = Between 5 and 7
7 = Unbearably severe- Symptoms are so bad, person can’t function all the time
**Question 2.** Assessment of non-nasal symptom severity (during the last week).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye symptoms</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Throat symptoms</td>
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<tr>
<td>Chronic cough</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ear symptoms</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental function</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Key to symptoms:**

1 = None- to an occasional limited episode  
2 = Between 1 and 3  
3 = Mild- Steady symptoms but easily tolerable  
4 = Between 3 and 5  
5 = Moderately Bothersome- Symptoms hard to tolerate, may interfere with activities of daily living and/or sleep  
6 = Between 5 and 7  
7 = Unbearably severe- Symptoms are so bad, person can’t function all the time
**Question 3.** Global assessment of nasal and non-nasal symptom severity (during the last week).

N.B. Please note Question 3 assesses your combined / overall nasal and non-nasal symptoms. Also, the scale is the reverse of the previous assessment scales: So “1” means severe; and “7” means no symptoms.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unbearable</td>
<td>Between 1 and 3</td>
<td>Moderately Bothersome</td>
<td>Between 3 and 5</td>
<td>Mild</td>
<td>Between 5 and 7</td>
<td>None to an occasional limited episode</td>
</tr>
</tbody>
</table>

Unbearable

No symptoms

Special key to Question 3 above:

1  =  **Unbearably severe**- Symptoms are so bad, person can’t function all the time
2  =  Between 1 and 3
3  =  **Moderately Bothersome**- Symptoms hard to tolerate, may interfere with activities of daily living and/or sleep
4  =  Between 3 and 5
5  =  **Mild**- Steady symptoms but easily tolerable
6  =  Between 5 and 7
7  =  **None**- to an occasional limited episode
**Question 4.** Quality-of-life assessment of rhinitis (hay fever) severity (during the last week).

![Scale from 1 to 7 with labels: Severely affected to Excellent.]

**Key to Quality of life:**

1 = Quality of life is terribly affected in terms of sleep disturbance at night and/or impairment of social and/or recreational activities.
2 = Quality of life is affected almost all the time in terms of sleep disturbance at night and/or impairment of social and/or recreational activities.
3 = Quality of life is affected often in terms of sleep disturbance at night and/or impairment of social and/or recreational activities.
4 = Quality of life is affected occasionally but it is tolerable in terms of sleep disturbance at night and/or impairment of social and/or recreational activities.
5 = Quality of life is hardly affected in terms of sleep disturbance at night and/or impairment of social and/or recreational activities.
6 = Quality of life is hardly noticed in terms of sleep disturbance at night and/or impairment of social and/or recreational activities.
7 = Excellent quality of life in terms of sleep disturbance at night and/or impairment of social and/or recreational activities.

**References:**
A2.5 Fortnightly Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

Rhinoconjunctivitis Quality of Life Questionnaire

PLEASE FILL IN THIS QUESTIONNAIRE BY TICKING [✓] THE APPROPRIATE BOX

ACTIVITIES
We would like you to think of ways in which your nose/eye symptoms trouble you in your life. We are particularly interested in activities that you do but which are limited by your nose/eye symptoms. You may be limited because you do these activities less often, or less well, or because they are less enjoyable. These should be activities which you do frequently and which are important in your day-to-day life. These should also be activities that you intend to do regularly throughout the study.

Here is a list of activities in which some people with nose/eye symptoms are limited. We hope that this will help you to identify the 3 most important activities in which you have been limited by your nose/eye symptoms during the last two weeks. Please fill in this form once a week.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BICYCLING</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>READING</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>SHOPPING</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>DOING HOME MAINTENANCE</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>DOING YOUR HOUSE WORK</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>GARDENING</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>WATCHING TV</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>EXERCISING OR WORKING</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>GOLF</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>USING A COMPUTER</td>
<td>25</td>
</tr>
<tr>
<td>11</td>
<td>MOWING THE LAWN</td>
<td>26</td>
</tr>
<tr>
<td>12</td>
<td>PLAYING WITH PETS</td>
<td>27</td>
</tr>
<tr>
<td>13</td>
<td>PLAYING WITH CHILDREN OR GRANDCHILDREN</td>
<td>28</td>
</tr>
<tr>
<td>14</td>
<td>PLAYING SPORTS</td>
<td>29</td>
</tr>
<tr>
<td>15</td>
<td>DRIVING</td>
<td>30</td>
</tr>
</tbody>
</table>
(1) SELECTED ACTIVITIES

Please write your 3 most important activities in the box below and then tell us how much TROUBLED you have been by each of these activities during the last two weeks as a result of your nose/eye symptoms by checking the box [X] with the appropriate rating. Once you have chosen the 3 activities, stick to them throughout the entire study, so we can monitor any changes, if any.

<table>
<thead>
<tr>
<th>Activities</th>
<th>Not troubled 0</th>
<th>Hardly troubled 1</th>
<th>Somewhat troubled 2</th>
<th>Moderately troubled 3</th>
<th>Quit a bit troubled 4</th>
<th>Very troubled 5</th>
<th>Extremely troubled 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>3.</td>
<td></td>
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</tr>
</tbody>
</table>

(2) SLEEPING

How TROUBLED have you been by each of these sleep problems during the last two weeks as a result of your NOSE/EYE SYMPTOMS?

<table>
<thead>
<tr>
<th>Sleep</th>
<th>Not troubled 0</th>
<th>Hardly troubled 1</th>
<th>Somewhat troubled 2</th>
<th>Moderately troubled 3</th>
<th>Quit a bit troubled 4</th>
<th>Very troubled 5</th>
<th>Extremely troubled 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Difficulty getting to sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Wake up during the night</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Lack of good night’s sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(3) NON-NOSE/EYE SYMPTOMS

How TROUBLED have you been by these problems during the last two weeks as a result of your NON-NOSE/EYE SYMPTOMS?

<table>
<thead>
<tr>
<th>Non-nose/eye symptoms</th>
<th>Not troubled 0</th>
<th>Hardly troubled 1</th>
<th>Somewhat troubled 2</th>
<th>Moderately troubled 3</th>
<th>Quit a bit troubled 4</th>
<th>Very troubled 5</th>
<th>Extremely troubled 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Thirst</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Reduced productivity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10. Tiredness</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>11. Poor concentration</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>12. Headache</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>13. Worn out</td>
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</tbody>
</table>

(4) PRACTICAL PROBLEMS

How TROUBLED have you been by each of these sleep problems during the last two weeks as a result of your NOSE/EYE SYMPTOMS?

<table>
<thead>
<tr>
<th>Practical problems</th>
<th>Not troubled 0</th>
<th>Hardly troubled 1</th>
<th>Somewhat troubled 2</th>
<th>Moderately troubled 3</th>
<th>Quit a bit troubled 4</th>
<th>Very troubled 5</th>
<th>Extremely troubled 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. Inconvenience of having to carry tissues or handkerchief</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Need to rub nose/eyes</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>16. Need to blow nose repeatedly</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
(5) NASAL SYMPTOMS

How TROUBLED have you been by each of these symptoms during the last two weeks?

<table>
<thead>
<tr>
<th>Nasal symptoms</th>
<th>Not troubled</th>
<th>Hardly troubled</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quit a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Stuffy/ blocked</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>18. Running</td>
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<tr>
<td>19. Sneezing</td>
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</tr>
<tr>
<td>20. Catarrh (drainage of mucous down the back of your nose)</td>
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</tr>
</tbody>
</table>

(6) EYE SYMPTOMS

How TROUBLED have you been by each of these symptoms during the last two weeks?

<table>
<thead>
<tr>
<th>Eye symptoms</th>
<th>Not troubled</th>
<th>Hardly troubled</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quit a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
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</thead>
<tbody>
<tr>
<td>21. Itchy eyes</td>
<td></td>
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<td></td>
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<td>22. Watering eyes</td>
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<tr>
<td>23. Sore eyes</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>24. Swollen eyes</td>
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</tr>
</tbody>
</table>
(7) EMOTIONAL

How TROUBLE have you been by each of these emotions during the last two weeks as a result of your NOSE/EYE SYMPTOMS?

<table>
<thead>
<tr>
<th>Emotional</th>
<th>Not troubled 0</th>
<th>Hardly troubled 1</th>
<th>Somewhat troubled 2</th>
<th>Moderately troubled 3</th>
<th>Quit a bit troubled 4</th>
<th>Very troubled 5</th>
<th>Extremely troubled 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. Frustrated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26. Impatient or restless</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. Irritable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. Embarrassed by your symptoms</td>
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<td></td>
</tr>
</tbody>
</table>

References:
A2.6 Weekly Rhinoconjunctivitis Quality of Life Questionnaire with

Standardised Activities/ RQLQ(S)

**Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities / RQLQ(S)**

PLEASE COMPLETE ALL QUESTIONS IN THIS QUESTIONNAIRE BY CIRCLING THE NUMBER DURING THE LAST WEEK AS A RESULT OF YOUR NOSE/EYE SYMPTOMS.

(1) ACTIVITIES
How TROUBLED have you been by each of activities during the last week as a result of your NOSE/EYE SYMPTOMS?

<table>
<thead>
<tr>
<th>Activities</th>
<th>Not troubled</th>
<th>Hardly troubled at all</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quit a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Regular Activities at Home and at Work (your occupation or tasks that you have to do regularly around your home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2. Social Activities (e.g., activities with your family and friends, playing with children and pets, sex, hobbies)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>3. Outdoor Activities (e.g., gardening, mowing the lawn, sitting outdoors, sports, going for a walk)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

(2) SLEEP
How TROUBLED have you been by each of these sleep problems during the last week as a result of your NOSE/EYE SYMPTOMS?

<table>
<thead>
<tr>
<th>Sleep</th>
<th>Not troubled</th>
<th>Hardly troubled at all</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quit a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Difficulty getting to sleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>5. Wake up during the night</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6. Lack of good night’s sleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
(3) NON-NOSE/ EYE SYMPTOMS

How TROUBLED have you been during the last week as a result these symptoms?

<table>
<thead>
<tr>
<th>Non-nose/eye symptoms</th>
<th>Not troubled</th>
<th>Hardly troubled at all</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quit a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Fatigue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>8. Thirst</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9. Reduced productivity</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>10. Tiredness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>11. Poor concentration</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>12. Headache</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>13. Worn out</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

(4) PRACTICAL PROBLEMS

How TROUBLED have you been by each of these problems during the last week as a result of your NOSE/EYE SYMPTOMS?

<table>
<thead>
<tr>
<th>Practical problems</th>
<th>Not troubled</th>
<th>Hardly troubled at all</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quit a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. Inconvenience of having to carry tissues or handkerchief</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>15. Need to rub nose/eyes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>16. Need to blow nose repeatedly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
(5) NASAL SYMPTOMS

How **TROUBLED** have you been by each of these symptoms during the **last week**?

<table>
<thead>
<tr>
<th>Nasal symptoms</th>
<th>Not troubled</th>
<th>Hardly troubled at all</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quit a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Stuffy/ blocked</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>18. Runny</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>19. Sneezing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>20. Post nasal drip</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

(6) EYE SYMPTOMS

How **TROUBLED** have you been by each of these symptoms during the **last week**?

<table>
<thead>
<tr>
<th>Eye symptoms</th>
<th>Not troubled</th>
<th>Hardly troubled at all</th>
<th>Somewhat troubled</th>
<th>Moderately troubled</th>
<th>Quit a bit troubled</th>
<th>Very troubled</th>
<th>Extremely troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. Itchy eyes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>22. Watering eyes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>23. Sore eyes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>24. Swollen eyes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
(7) EMOTIONAL

How often during the last week have you been TROUBLED by these emotions as a result of your NOSE/EYE SYMPTOMS?

<table>
<thead>
<tr>
<th>Emotional</th>
<th>None of the time</th>
<th>Hardly any time at all</th>
<th>A small part of the time</th>
<th>Some of the time</th>
<th>A good part of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. Frustrated</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>26. Impatient or restless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>27. Irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>28. Embarrassed by your symptoms</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

References:

# A2.7 Records of Medication Usage

## Records of Medication Taken

**During Last Week For Your Hay Fever**

*Note:* Fill in one row only everyday. When completed, return this form to your assessor and get a new one for the next week.

<table>
<thead>
<tr>
<th>Day/week</th>
<th>Date</th>
<th>Day</th>
<th>Morning: A</th>
<th>Between: B</th>
<th>Night: C</th>
<th>Name of Medication</th>
<th>Dose</th>
<th>Frequency</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td></td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note:* If you change medication and/or dose, please explain the reason in the **Remark** column.
A2.8 Records of Ear-acupressure Dosage

School of Health Sciences  Chinese Medicine Research Group

RECORDS OF EAR-ACUPRESSURE DOSAGE

Please tick the cell using “\” that represents the number of pellets left on your ear every day.

<table>
<thead>
<tr>
<th>Day/week</th>
<th>Date</th>
<th>Day</th>
<th>Number of pellets still stuck to your ear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A2.9 Adverse Event Record Form

Please record any unexpected feelings, signs and symptoms **during the last week** in this study.

<table>
<thead>
<tr>
<th>Event (Please describe the symptoms; how it affects you)</th>
<th>When did it begin (date &amp; time)</th>
<th>When did it stop (date &amp; time)</th>
<th>Intensity (1,2, or 3)</th>
<th>Relationship to ear-acupressure (1, 2, 3, or 4)</th>
<th>Severe adverse events * (Yes/No)</th>
</tr>
</thead>
</table>

**Intensity:**
1 = **mild** (easily tolerated by patient, causing minimal discomfort)
2 = **moderate** (discomfort significant enough to interfere with daily activities)
3 = **severe** (incapacitating and/or requiring therapeutic intervention)

**Relationship to ear-acupressure:**
1 = unrelated 2 = possibly 3 = probably 4 = definitely

* **Severe adverse events:** defined as potential to be fatal, life threatening, permanent incapacitating or resulting in hospitalisation.
A2.10 Participants’ Opinion of Ear-acupressure Credibility Expectancy

Questionnaire

Participants’ Opinion of Ear-acupressure
Credibility Expectancy Questionnaire

We would like you to indicate below how much you believe, right now, that the treatment you are receiving will help you to reduce your hay fever symptoms. Belief usually has two aspects to it: (1) what one thinks will happen and (2) what one feels will happen. Sometimes these are similar, sometimes they are different. Please answer the questions below. In the first set, answer in terms of what you think. In the second set answer in terms of what really and truly feel.

SET I

1. At this point, how logical does the treatment offered you seem?

<table>
<thead>
<tr>
<th></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>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Somewhat logical</td>
<td>Very logical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. At this point, how useful do you think the treatment will be in reducing your hay fever symptoms?

<table>
<thead>
<tr>
<th></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>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all useful</td>
<td>Somewhat useful</td>
<td>Very useful</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. How confident would you be in recommending this treatment to a friend who experiences similar problems?

<table>
<thead>
<tr>
<th></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>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Somewhat</td>
<td>Very much</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. By the end of the therapy period, how much improvement in your hay fever symptoms do you think will occur?

<table>
<thead>
<tr>
<th></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>
</tr>
</thead>
<tbody>
<tr>
<td>None at all</td>
<td>Total Improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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SET II

For this set, close your eyes for a few moments and try to identify what you really feel about the treatment and its likely success. Then answer the following questions.

1. At this point, how much do you really feel that therapy will help you to reduce your hay fever symptoms?

   1  2  3  4  5  6  7  8  9
   Not at all useful  Somewhat useful  Very useful

2. By the end of the therapy period, how much improvement in your hay fever symptoms do you really feel will occur?

   1  2  3  4  5  6  7  8  9
   Not at all  Somewhat much  Very much

References:

Additional Question:

For the assessment of the effectiveness of the blinding procedure we used in this study, please indicated that the treatment that you believe you have received is (please √):

- □ Real ear-acupressure treatment
- □ Sham ear-acupressure treatment
- □ Not sure
Appendix three: Treatment effects for Pilot study II

A3.1 Juniper 4 point symptom scores for Pilot study II

![Juniper TNSS Graph]

![Juniper Sneezing Graph]

![Juniper Blocked Nose Graph]
A3.2 Spector 7 point VAS for Pilot study II

**Spector VAS Sneezing**

**Spector VAS Runny Nose**

**Spector VAS Congestion**
A3.3 RQLQ 7 domains for Pilot study II

RQLQ(S) Activities domain

RQLQ(S) Sleep domain

RQLQ(S) Non Nose/eye Symptoms domain
Appendix four: Published journal articles

A4.1 Publication 1


Chinese Medicine

Commentary

Recent developments of acupuncture in Australia and the way forward
Charlie Changli Xue*, Anthony Lin Zhang, Angela Weihong Yang,
Claire Shuiping Zhang and David Frederick Story

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Abstract
Almost one in ten Australians has received acupuncture treatment by acupuncturists and/or medical doctors in private clinics. The majority of Australian health insurance funds offer rebates for acupuncture. Statutory regulations for acupuncture have been implemented in the State of Victoria, Australia. Six acupuncture degree courses have been approved by the Chinese Medicine Registration Board of Victoria and/or accredited by the Australian Acupuncture and Chinese Medicine Association. Furthermore, a number of clinical trials of acupuncture on allergic rhinitis, pain and women’s health were carried out in Australia. Recent developments of acupuncture in Australia indicate that through adequate and appropriate evaluation, acupuncture begins to integrate into mainstream health care in Australia.

Background
The history of acupuncture in Australia can be traced back to the 1850s when the first Chinese immigrants arrived and worked in the gold fields of Australia [1]. Acupuncture is now considered as the general public as one of the most popular treatments of complementary and alternative medicine (CAM) [2].

There have been four developmental stages of acupuncture in Australia. (1) Self-management stage (1850s–1960s): Acupuncture was a form of unregulated health care. (2) Professional development stage (1970s–1980s): Acupuncture associations were established to promote the acupuncture profession and facilitate clinical practices. (3) Standard-setting stage (1990s): Universities and private colleges started offering acupuncture training. Acupuncture became an established modality of CAM in Australia [3]. (4) Regulation stage (2000 onwards): The practice of acupuncture is subject to mandatory registration in the State of Victoria, Australia as stipulated by the Chinese Medicine Registration Act 2000 [4] which was superseded by the Health Professions Registration Act 2005 [5].

Here, we highlight the recent developments of acupuncture in terms of clinical practices, education, research and regulations in Australia and illustrate how acupuncture is being integrated into mainstream health care in Australia.

**Background:** Allergic rhinitis affects 10–40% of the population globally with a substantial health and economic impact on the community.

**Objective of review:** To assess the effectiveness and safety of ear-acupuncture or ear-acupressure for the treatment of allergic rhinitis by reviewing randomised controlled trials and quasi-randomised controlled trials.

**Type of review:** This review followed the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions.

**Search strategy:** A total of 21 electronic English and Chinese databases were searched from their respective inceptions to April 2008. Key words used in the search included the combination of ear, auricular, acupuncture, acupressure, acupoint, allergic, allergy, rhinitis, hayfever, randomised clinical trial and their synonyms.

**Evaluation method:** The methodological quality was assessed using Jadad's scale. The effect size analysis was performed to explore the difference between interventional groups.

**Results:** Ninety-two research papers were identified and seven of them referring to five studies met the inclusion criteria. All included studies involved ear-acupressure treatment. These studies mentioned randomisation, but no details were given. None of the five studies used blinding or intention-to-treat analysis. Ear-acupressure was more effective than herbal medicine, as effective as body acupuncture or antihistamine for short-term effect, but it was more effective than antihistamine for long-term effect.

**Conclusions:** The benefit of ear-acupressure for symptomatic relief of allergic rhinitis is unknown due to the poor quality of included studies.

Allergic rhinitis, including seasonal allergic rhinitis and perennial allergic rhinitis, is an inflammatory condition involving the nasal mucous membrane. Allergic rhinitis sufferers account for 10–40% of population globally and the prevalence has increased in the last few decades. In Australia, allergic rhinitis is one of the most common long-term conditions and in recent years, the proportion of adults with allergic rhinitis in Australia has increased from 13.9% in 1995 to 16.1% in 2004–05. Allergic rhinitis has a significant impact on quality of life, work/school performance and productivity. It causes a significant economic burden as well. Allergic rhinitis is associated with asthma, sinusitis and other co-morbidities, such as conjunctivitis.

The current management of allergic rhinitis includes avoidance of exposure to allergens, pharmacological treatment, immunotherapy and patient education. Medications include oral and topical histamine H1 receptor antagonists, topical and systemic glucocorticosteroids, decongestants, topical anti-cholinergics, antiallergy and oral anti-allergic drugs. However, these medications are associated with certain undesirable side-effects and, frequently, do not provide complete symptomatic relief. In recent years, there is a worldwide trend among allergic rhinitis sufferers to seek complementary and alternative medicine (CAM) treatment with a number of systematic reviews that evaluate the therapeutic benefits of herbal medicine and acupuncture. Specifically, acupuncture has been demonstrated to be effective for seasonal allergic rhinitis and perennial allergic rhinitis, while Chinese herbal medicine has also been shown to be beneficial for seasonal allergic rhinitis and perennial allergic rhinitis. The cost-effectiveness of acupuncture treatment of perennial allergic rhinitis was also evaluated in a large-scale trial. It was demonstrated in terms of an international benchmark namely the cost per
A4.3 Publication 3