University of Alberta

Traditional Chinese Medicine:
Evidence and Challenges in Fatigue Clinical Research

by

Denise Lauren Adams

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Public Health Sciences

Spring 2010
Edmonton, Alberta

Examining Committee

Sunita Vohra, Pediatrics

Yutaka Yasui, Public Health Sciences

Wendy Vaudry, Pediatrics

Steven Aung, Medicine

Jean-Paul Collet, Pediatrics, University of British Columbia

Leonard Jason, Psychology, DePaul University

Dedication

This body of work is dedicated to my family.
Without your patience, support, and love this would not have been possible.

Abstract

The increasing popularity of traditional Chinese medicine (TCM) therapies as health care options warrants thorough examination of the efficacy and safety evidence around these therapies. This thesis explores the intersection of TCM and fatigue using two rigorous methodologies: systematic reviews (SRs) and a randomized controlled clinical trial (RCT). In order to inform the development of an RCT of acupuncture for infectious mononucleosis (mono), a common condition with no known cure, characterized by profound fatigue, we examined the literature on TCM treatment of mono as well as another fatigue condition, idiopathic chronic fatigue (ICF). Additionally, we investigated the literature on the safety of pediatric acupuncture.

SRs of TCM efficacy in mono and ICF determined that although clinical trials exist, methodological flaws compromised their validity. In particular, studies published as RCTs were found to lack proper randomization. Inclusion of these studies in the SRs would have been inappropriate and demonstrates the importance of verifying RCT methods.

We also present the results of the first known SR of pediatric acupuncture safety. This review was comprehensive, including a large number of databases and publications in any language. Synthesis of the results from those studies that included a denominator produced mild adverse event estimates of 16.3/100 (95% CI 11.2–21.5) per patient, for RCTs, and 6.3/100 (95% CI 4.9–7.7) per patient, for cohort studies, with a combined estimate of 7.8/100 (95% CI 6.4–9.2) per patient.

We developed and conducted an RCT of acupuncture for mono, although

limitations to recruitment resulted in the enrolment of only three participants. The primary result of the small sample size was to restrict the determination of treatment effect, however, successful implementation of other elements is informative to further research in this area. In addition, we determined the local 5-year Monospot positive incidence rate to be 1.11/1000 (95% CI 0.95–3.2) for all ages and 5.46/1000 (95% CI 0.89–10.0) for the 15-25 year old group.

This dissertation examined the evidence around TCM and fatigue and provides recommendations that are aimed at increasing the value of research and the safety and efficacy of practice in this area.

Table of Contents

Chapter 3: The Safety of Pediatric Acupuncture: A Systematic Review

Chapter 4: A Pragmatic Randomized Controlled Trial of Acupuncture Therapy for Infectious Mononucleosis

Chapter 5: Summary, Conclusions, and Implications

List of Tables

List of Figures

Chapter 1: Overview

1.1 Purpose of Dissertation

This dissertation explores the intersection of two bodies of knowledge, traditional Chinese medicine (TCM) and fatigue-related medical conditions, specifically, chronic fatigue syndrome (CFS) and infectious mononucleosis (mono), through the current gold standards in clinical epidemiology: systematic reviews (SRs) and randomized controlled trials (RCTs).

The original goal was to conduct an RCT of TCM, as a whole system, in which patients with acute mono would be assigned to treatment by a TCM practitioner or a conventional medicine practitioner, each of whom would be free to utilize any products or practices from their respective disciplines. As TCM therapies are often administered together, in a system of care, rather than as individual modalities, this approach was intended to allow the evaluation of TCM treatment, as a system, rather than as individual modalities. Discussion with Health Canada, the regulatory body in charge of clinical trials that involve drugs or natural health products in Canada, suggested that a trial including TCM herbs would likely involve an approval process of many months and even years (personal communication, Health Canada). Because this timeframe was prohibitive for completion of a PhD project, it was decided to limit the RCT protocol and focus on acupuncture as the primary treatment.

In exploring the medical literature relevant to setting up such an RCT, a series of SRs were conducted to evaluate available data regarding efficacy and safety. In the first SR, publications involving treatment of mono with TCM modalities were sought. Due to the limited availability of such data, a second SR of TCM modalities was conducted, focusing on chronic fatigue syndrome, a condition for which mono may be a contributing factor. It was hoped that these two searches would contribute to the set up of the RCT. The conduct of these two SRs identified numerous methodological issues that are worthy of further study and which must be resolved in order to strengthen research, both in the area of TCM and in health care in general.

Additional background material, in the area of pediatric safety of acupuncture, was also thought to be important to building the RCT. Extensive acupuncture safety information exists for adults, however, a SR of pediatric safety had not yet been conducted, a gap that this dissertation attempts to fill. The interrelation of the components of this dissertation is shown in figure 1.1.

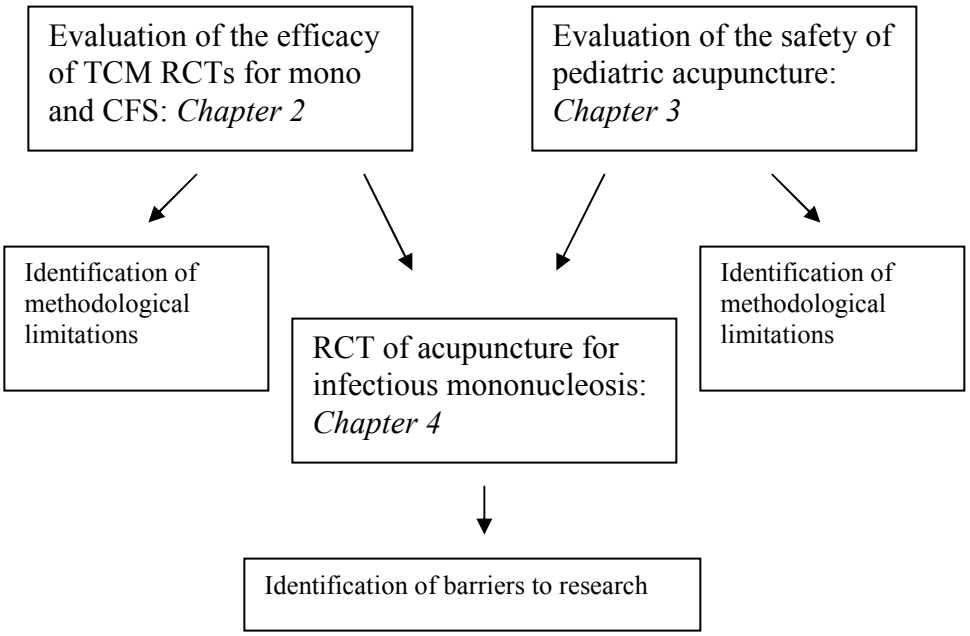

Figure 1.1: Interrelations of Dissertation Components

The next section will introduce TCM, briefly describing principles and practices, and then providing an in-depth discussion of acupuncture, a therapy that figures prominently in future chapters. Following descriptions of fatigue, chronic fatigue and infectious mononucleosis, discussion will focus on what is known about treatment of these conditions with TCM.

1.2 Background Material

1.2.1 Traditional Chinese Medicine: Principles and Practices

TCM encompasses numerous health care therapies that evolved in China over hundreds or thousands of years. Basic tenets of TCM are rooted in ancient texts such as the Yellow Emperor's textbook of medicine (Huang Di Nei Jing) that is thought to date back to approximately 200 B.C. (Stux 1988). TCM has been estimated to be used for primary health care in China by 40% of the population (WHO 2002) and by over 25% of the world's population (Flaws 1993). Recent reports from Western countries support the notion that the use of TCM for health care has become global (Barnes 2008, Statistics Canada 2004, Zhu 2009).

The TCM approach to health and healing differs from Western medicine in that disease is believed to be the result of imbalance and disharmony between organ systems in the body, between the body and the environment, or in the flow of the body's "vital energy", also known as Qi. The goal then is to restore balance and harmony and to strengthen and support the body's innate healing capacities (Flaws 1993). This concept of balance in TCM is often described in terms of yin and yang, which can be described as opposing but complementary and interdependent states or forces that are present in and act on all things. The use of these concepts can be applied to all areas, including natural phenomena where yin refers to darkness, the moon, rest, earth, flat, space, West, North, right, substantial, matter, contraction, etc and yang refers to light, the sun, activity, heaven, round, time, East, South, left, insubstantial, energy, expansion, etc. These terms also apply to the body and states of health, where yin refers to front, interior, structure, chronic disease, gradual onset, cold, pale, listless, etc and yang refers to back, exterior, function, acute disease, rapid onset, heat, redness, restless, etc (Aung 2007, Maciocia 1989).

TCM patient diagnosis is complex and dynamic. Diagnosis is based on the belief that signs and symptoms directly reflect the condition and function of internal organs and systems. Elements of diagnosis include appearance of the skin, visual examination of the size, color, and coating of the tongue, palpation of

six separate pulses in the wrists, emotional state and demeanour of the patient, smells and sounds (Aung 2007, Maciocia 2004). The etiology of disease is not relevant to treatment, which is instead based on the presentation of patterns of symptoms. Patterns of symptoms may be as numerous as the patients who present them and are not tied to disease classifications. Patients with the same disease classification may present different patterns, while patients with different diseases may present the same pattern. Patterns of symptoms may be classified into syndromes, which dictate the treatment principles (the action that the treatment is meant to evoke in the body) that the practitioner should follow to achieve optimal health, and are often described in terms of the balance of Qi, yin and yang, such as stagnation, deficiency, or excess. Imbalance of yin/yang may be addressed by a treatment principle such as increasing or strengthening (tonification) where deficiency exists or elimination in the case of excess (Aung 2007, Maciocia 1989). Further categorization of syndromes may occur at the level of the organ system, according to the concepts of Zang Fu, in which diagnosis would specify where imbalance is occurring (i.e. deficiency of liver Qi) (Aung 2007, Stux 1988).

Treatment under TCM is customized to individual patient needs, as presented at each session; diagnosis, treatment principle and treatment factors may vary between sessions (Kaptchuk 2002). Therapies recognized as part of TCM may be applied singly or in combination and include, but are not limited to:

i) Medicinal products (plants/animals/minerals): preparation and consumption or application of product to the body (singly or in combination);
ii) Energy (Qi) manipulation: including internal manipulation (the practice of Qi Gong by the patient) and external manipulation (the application of external Qi to the patient by the practitioner);
iii) Tui-na: physical manipulation of the body;
iv) Dietary recommendations: such as avoidance or increased consumption of certain spices or foods;
v) Therapeutic exercise: including tai chi;

vi) Acu-point stimulation: selection and stimulation of acu-points along defined meridians; stimulation may occur through needling (acupuncture), pressing (acupressure), laser (laser acupuncture), electric current (electro acupuncture), injection of chemicals into acu-points, and/or application of moxa (moxibustion).

1.2.1.1 Acupuncture: Technique versus Whole System of Care

Acu-points refer to precisely defined, specific points on meridians (or channels) that lie along the surface of and within the body. Each meridian has a distinct name that is based on association with important body systems (Stomach, Spleen, Kidney, Heart, Conception Vessel (midline along the back of the body), and Governing Vessel (midline along the front of the body), for example). Stimulation of acu-points may be accomplished through a variety of methods including application of heat, pressure, laser, electric current, or insertion of thin needles (Flaws 1993). According to Chinese philosophy acu-point stimulation is believed to correct and rebalance the body's Qi, which flows through the meridians. When blockages in the flow of Qi occur, illness results. Each acu-point has defined therapeutic actions; some points treat broad imbalances while others treat local symptoms. The technique of acupuncture (stimulation using insertion of needles) may be varied according to the following factors: specific point selected, number of points selected per treatment session, depth of needle insertion, presence and mode of needle manipulation (i.e. by touch, heat, or electric current), length of treatment time, the need for tonification versus removal of excess, and achievement of de chi (a sensation felt upon insertion of the needle, thought to indicate correct positioning in the active point). Treatment decisions regarding these factors are based on patient diagnosis and principle of treatment (Aung 2007, Kaptchuk 2002). Studies that focus on the specific effects of acu-point stimulation are common in the acupuncture research literature, however, acupuncture can also be thought of as a system of care, which includes stimulation of acupoints as well as other elements, including consultation and diagnostic processes, patient and practitioner beliefs and expectations of

acupuncture, practitioner skill, patient-practitioner relationship, physical setting and devices, protected time and attention from the practitioner, individualized treatment, and interaction of the aforementioned elements (Kaptchuk 2002, Paterson 2004, Paterson 2005, Thomas 2006, White 2001). Research into acupuncture has approached it both as a technique (Berman 1999, Kleinhenz 1999, Melchart 2005, Schneider 2006) and as a system of care or complex intervention (Borud 2009, Brinkhaus 2008, Salter 2006, Thomas 2006). The research question, methods, including choice of control group, and outcomes are influenced by which view of acupuncture the researcher is investigating. Further discussion of whole systems research can be found in chapter 4.

1.2.1.2 Prevalence of Acupuncture Use

Acupuncture is a popular treatment modality in many parts of the world. Canadian figures indicate that 12% of the population has ever used acupuncture (York University 1999) and that 2% used acupuncture in 2003 (Statistics Canada 2004). Recent US data shows that in 2007, over 3.1 million adults used acupuncture, up from over 2.1 million in 2002 (Barnes 2008). Use among specific patient populations is frequently much higher, including over 2% of people with chronically fatiguing illnesses (Jones 2007, Lee 2004, Rosenberg 2008).

1.2.1.3 Safety of Acupuncture

Studies on the safety of acupuncture have been conducted, however, none have specifically reported on the safety of pediatric acupuncture. In a 2005 study of over 9400 consecutive adult patients, short-term reactions to acupuncture were collected, both positive and negative. Of the 15 745 reactions reported, 68% were positive and included feeling relaxed and energized while 18% were negative and included ache, pain, discomfort or bleeding, bruising, feeling faint or dizzy, worsening of condition, and nausea; 14% of reports were of tiredness or drowsiness. Only 13 (0.14%) patients were unwilling to have acupuncture again because of short-term reactions (Macpherson 2005). In 2004, a meta-analysis reviewing safety data from 12 prospective studies, conducted between 1988 and

2004, that included over one million treatment sessions in more than 100 000 patients, concluded that the risk of serious adverse events (AEs) associated with acupuncture was five per one million treatments. The serious AEs that were reported in these studies included four cases of pneumothorax and two cases of broken needles (White 2004). The populations of four of the studies included both children and adults (Chen1990, Umlauf 1988, Yamashita 1999, Yamashita 2000), while two others did not (Ernst 2003, Odsberg 2001); for six studies, no information about the age of the populations was available (MacPherson 2001, Melchart 1995, Melchart 1996, Melchart 1998, Melchart 2004, White 2001, Yong 1999). None of the reviews reported the ages of the patients in whom AEs occurred, however, where the study population age information was known, the proportion of children was low (i.e. 5.0 % under 20 years (Yamashita 1999), 5.5% under 15 years (Umlauf 1988)). Other population information suggests few children were included in some of the other studies (i.e. 16% under 40 years (Yong 1999), mean 55 years +/- 15.5 (Melchart 2004). The occurrence of events classified as 'significant but minor' (defined as unusual, novel, dangerous, significantly inconvenient, or requiring more information), such as seizure, broken or forgotten needles, or unexpected and prolonged aggravation of symptoms, has also been collected. Estimates ranged from 13/10 000 to 14/10 000 treatment sessions despite the fact that three different forms of acupuncture were used, traditional Chinese acupuncture, Western medical acupuncture, and Japanese acupuncture (MacPherson 2001, White 2001, Yamashita 1999). There is general consensus that acupuncture is safe if performed by appropriately trained practitioners (BMA 2000, Leung 2008, NIH 1997, Weidenhammer 2007, WHO 2002, Yamashita 1999, Yamashita 2008).

1.2.1.4 General Efficacy of Acupuncture

The efficacy of acupuncture has been the subject of many reviews and meta-analyses (Afari 2003, Berman 2000, Birch 2004, Dincer 2003, Jindal 2008, Kaptchuk 2002, Leggett Tait 2002, Lewith 1983, Mayer 2000, Sanchez Araujo 1998, WHO 2002). In a 2002 report, the World Health Organization listed 28

conditions that can be treated with acupuncture and over 40 conditions for which acupuncture has shown a therapeutic effect (WHO 2002). More rigorous examinations of the clinical acupuncture research have reported that acupuncture was effective for nausea, dental and TMD pain and encouraging for headaches, fibromyalgia, osteoarthritis, low back pain, and some gynaecological and mental health disorders (Brooks 2001, Jindal 2008, Park 2008).

Although the conclusions of these reviews and reports vary with respect to the number and type of conditions found to respond to acupuncture, all comment on the dearth of high quality research into the efficacy of acupuncture. The results of clinical studies of acupuncture have seldom been consistent, in part because of the wide range of acupuncture practices and techniques used as well as inconsistency of study design and conduct. Two commonly cited problems are the variation in control group and the current lack of an inert control for acupuncture needling, which is the most frequently researched form of acu-point stimulation (Berman 2000, Kaptchuk 2002, Lewith 1983, Mayer 2000, Park 2008, Sanchez Araujo 1998, Vickers 2002). The latter issue is discussed in detail below.

1.2.1.5 Acu-point Stimulation Control Techniques

Method of stimulation is the element of acu-point treatment that is most often controlled for in clinical research focusing on acupuncture as a technique rather than as a system of care. In the examination of the specific effects of acu-point stimulation, blinding or masking of the intervention as well as use of a similar control technique may be desired in order to reduce or remove bias resulting from knowledge of the intervention. Some stimulation techniques are relatively simple to develop controls for (i.e. use of inactive laser versus active laser stimulation) while others are more difficult (i.e. needle stimulation). Clinical trials investigating needle acupuncture have employed a range of control techniques. These may be categorized as penetrating (those that penetrate the skin) and non-penetrating (those that do not penetrate the skin). Examples of penetrating control methods include deep insertion of needles at acu-points not thought to influence the condition under study or at points that are not considered

to be active acu-points, and minimal acupuncture where needles are superficially inserted into the skin using either of the two previous methods of point selection. Penetrating controls have been shown to produce physiological effects not unlike true acupuncture (White 2006). These methods may be useful for investigating factors such as point location, penetration depth, and method of needle manipulation but are not suitable as controls for needle penetration (Birch 2006, Vickers 2002). Non-penetrating controls have been proposed as more useful for investigating effects of needle penetration, however, studies have shown that these methods are also not 'inactive' (Streitberger 2004, White 2001, White 2006). Examples of non-penetrating controls include the Park Sham Device (PSD) (Park 2002), the Streitberger Needle (SN) (Streitberger 1998), and a variety of less formal and less standardized methods (Tough 2009, White 2001). Descriptions of these methods are presented in table 1.1. The PSD and the SN have been standardized, validated, and used in a variety of clinical trial populations (Kaptchuk 2006, Kleinhenz 1999, Lao 1999, Martin 2006, Park 2005, Smith 2007). Both methods employ a rigid material (tube or ring) that is adhered to the skin. The tube or ring act as a guide and restraint for either a real or a sham needle designed to retract into the handle, producing the illusion of penetration. Both sham needles press and prick the skin rather than penetrate it. These devices are limited in application to areas where adhesion of a rigid material is possible. Areas identified as inappropriate include hair (i.e. scalp), narrow or bony sections (i.e. joints, digits), and ears (Kaptchuk 2006, Park 2002). Requirements for use of adhesive sham controls in a clinical trial include a priori acu-point selection or restriction so that only points amenable to adhesive sham are utilized.

Table 1.1: Acupuncture Controls – Non-penetrating Devices

Device	Description
Park Sham Device (PSD)	Made up of an adhesive tube containing either a real or sham needle that retracts into the handle when pressure is applied. This device produces the sensation of penetration but does not in fact penetrate the skin; retraction of the needle gives the illusion of penetration.
Streitberger Needle (SN)	Similar in design to the PSD. It is composed of an adhesive ring through which a real or sham needle is fixed using a small bandage. The function and sensations produced by the SN are similar to the PSD.
Blunt tool	Includes use of a fingernail, toothpick, blunt needle, or other blunt instrument to produce 'acupuncture' sensation with or without the subsequent attachment, using an adhesive material, of a bent needle in order to produce the illusion of penetration.

1.2.1.6 Acupuncture: Choice of Intervention for Research

Clinical acupuncture studies are currently carried out in one of two ways, as research into the specific effects of acu-point stimulation or research into how acupuncture, as a system, compares to another system of care, often conventional medicine. The research question of interest is critical in determining which approach to take. Examples of research questions for which the first approach may be more appropriate include "Is deep needle penetration more effective in increasing range of motion in patients with osteoarthritis of the knee, than shallow penetration at the same acu-point?" and "Is traditional Chinese needle acupuncture at PC 6 more effective than sham acupuncture in reducing chemotherapy induced vomiting?" In addition to standard methodological features such as randomization, allocation concealment, and use of objective outcomes where possible, the study design for both of these questions could include blinding if desired. In this way, the specific effects of the acu-point stimulation

under examination may be isolated away from other effects and quantified. In contrast, studies examining acupuncture as a system of care may ask questions such as "Does the addition of acupuncture therapy to conventional care reduce rhinitis in seasonal hay fever, as compared to conventional care alone?" or "Is acupuncture therapy as effective as physiotherapy in treating low back pain?" In these examples, no attempt is made to blind the intervention, as the non-specific effects, including those related to knowledge of the intervention, are considered as part of the overall effect. A design that is often used to evaluate the comparative effectiveness of interventions in routine practice is the pragmatic (or practical) clinical trial (PCT) (Blackwood 2006, MacPherson 2004, Paterson 2005). Further discussion of the PCT can be found in chapter 4.

1.2.2 Fatigue

Fatigue may be described as a pervasive sense of tiredness or lack of energy that is not related exclusively to exertion. Community prevalence estimates in different countries range up to 50%, with prevalence in primary care reported at up to 40% (Buchwald 1995, Ranjith 2005, Skapinakis 2000, Skapinakis 2003, Wessely 1999). Fatigue may result from behavioral problems such as excess physical or mental activity, sleep deprivation, and poor diet or a range of medical conditions including infection, and cardiovascular, metabolic, connective tissue and endocrine disorders (De Merlier 2003). Fatigue may be of known or unknown etiology and ranges in duration from short-term to chronic. The more severe forms of fatigue include idiopathic chronic fatigue (ICF) and chronic fatigue syndrome (CFS) (Fukuda 1994). The interrelationship of fatigue conditions is shown in figure 1.2.

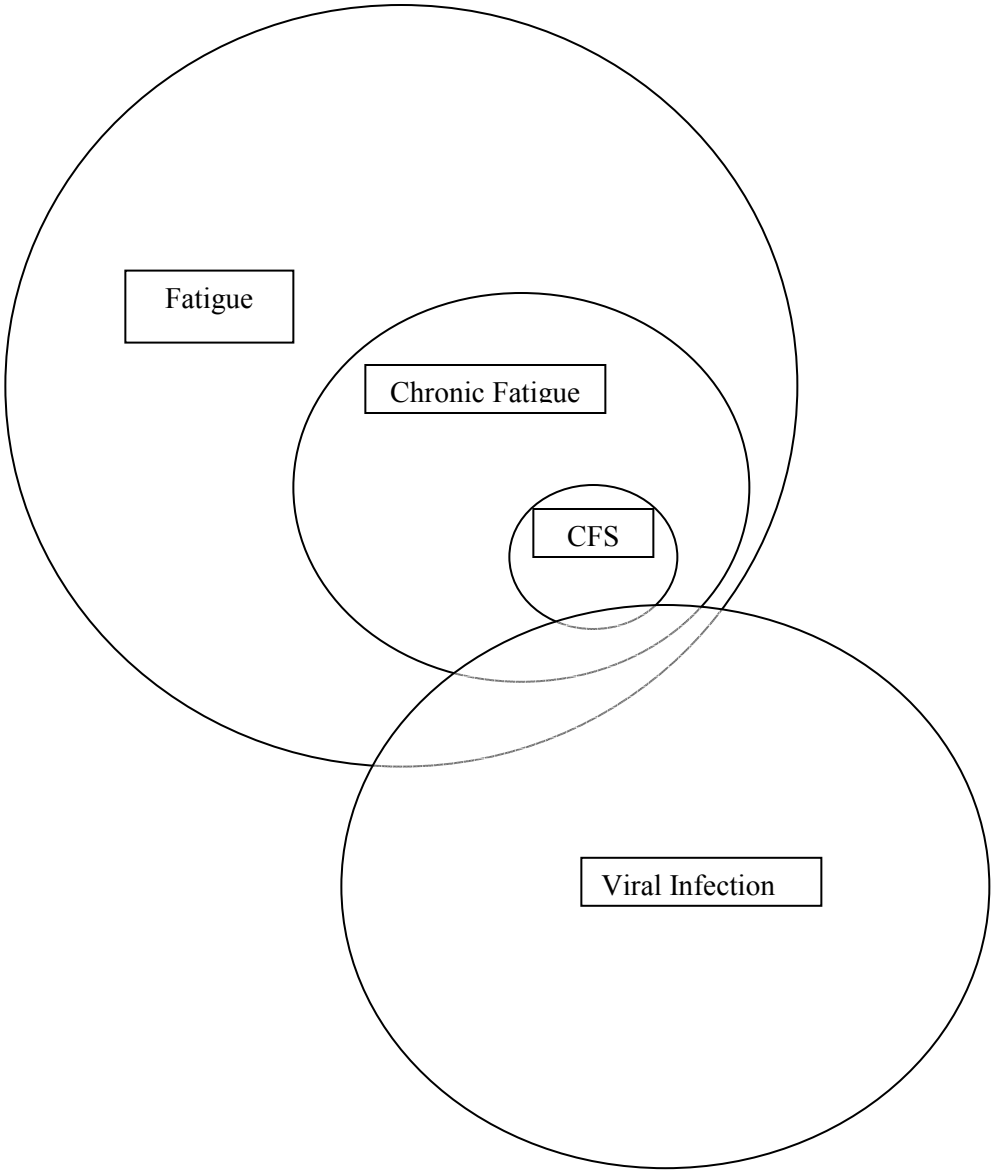

Figure 1.2: Interrelation of Fatigue Conditions

1.2.2.1 Chronic Fatigue: ICF/CFS

CFS is characterized by severe disabling fatigue and a combination of four additional symptoms that may include impairments in cognitive or neurological function, sleep dysfunction, musculoskeletal pain, and endocrine or immune dysfunction. Additionally, all known medical and psychiatric causes must have been ruled out and the condition must have been present for at least six months (Fukuda 1994). ICF meets all of the criteria for CFS except for the need for four additional symptoms (Fukuda 1994). ICF/CFS has been identified by many names

throughout its documented history; current terminology also varies depending on global region and diagnostic criteria. Some of the names that may be used to describe ICF/CFS or its subtypes include neurasthenia, post-viral fatigue syndrome, chronic fatigue immune deficiency syndrome (CFIDS), and myalgic encephalomyelitis (ME) (Patarca-Montero 2004, Taylor 2003).

1.2.2.2 Prevalence, Burden and Prognosis of ICF/CFS

Estimates of prevalence vary depending on the target population, study methodology, and diagnostic criteria, however, prevalence of CFS in North America has generally been accepted to be 0.2-0.4% of adults in the general population, with the age range of 30-50 years most commonly affected (Afari 2003, Bierl 2004, Carruthers 2003, Jason 1999, Taylor 2003). The US Centers for Disease Control and Prevention estimates that between one and four million Americans suffer from CFS (CDC 2009). Community prevalence of ICF is less well documented but is believed to be much higher (Buchwald 1995, Darbishire 2003, Jason 1999, Ranjith 2005, Skapinakis 2000, Taylor 2002, Taylor 2003, Wessely 1997). The prevalence of ICF and CFS in primary care has been reported as 9% and 2.6%, respectively (Wessely 1997). Considerable disability and public health burden are associated with ICF/CFS. The impact of these conditions is not only physical in nature but extends to psychological, social, emotional, and economic dimensions as well. Approximately 26% of ICF and 37% of CFS patients are unable to work (Bombardier 1996). Cost estimates in Britain determined that each case of ICF/CFS in adults cost an average of £1 906 over three months in informal health care and lost productivity (McCrone 2003). Similar estimates in the US reported annual individual and national losses of $20 000 and $9.1 billion (USD), respectively (Reynolds 2004). The prognosis of ICF and CFS is often poor and longitudinal studies have reported that less than 30% of ICF and 10% of CFS patients fully recover (Cairns 2005, Joyce 1997, Taylor 2002).

1.2.2.3 Treatment of ICF/CFS with Conventional Medicine

There is currently no cure for ICF/CFS. Treatment options that are used in clinical practice are directed toward relieving symptoms and improving function and include pharmacological, immunological, and antiviral agents, cognitive/behavioural therapies, and physical therapies, although few clinical studies have been published for any of these options (Afari 2003, Levine 2003, Rimes 2005). Recent evaluation of the levels of evidence for the various treatment options reported that with the exception of one pharmacologic agent for immune dysfunction, all of the treatments reviewed ranked in the lowest levels of evidence (expert opinion of an individual or committee) (Carruthers 2003). While factors such as unclear etiology, heterogeneity in presentation, and lack of established treatments make development of treatment recommendations difficult (Afari 2003), several countries have prepared CFS management guidelines, including Canada, the USA, and the UK (Carruthers 2003, CDC 2009, Turnbull 2007). The UK publication, prepared by the National Institute for Health and Clinical Excellence (NICE), is the most extensive and up-to-date of these (Turnbull 2007). The NICE guidelines state "There is no known pharmacological treatment or cure for CFS/ME. However, symptoms of CFS/ME should be managed as in usual clinical practice." Examination of specific therapies led to the conclusions that:

- No benefit was found for anticholinergic agents, antidepressants, antihypertensives, growth hormone, or antivirals such as acyclovir, gancyclovir, and inosine pranobex;
- Mixed results were reported for studies of oral NADH, melatonin, steroids, monoamine oxidase inhibitors, and immunological treatments such as interferon;
- Adverse events serious enough to cause withdraw from studies were reported for galanthamine hydrobromide, phenelzine, fludrocortisone, and fluoxetine.

In a similar examination of the evidence around complementary and alternative medicine (CAM) treatments for CFS the authors concluded that there was insufficient evidence for the use of dietary supplements including vitamin B12, vitamin C, co-enzyme Q10, magnesium, NADH, or multivitamins and minerals (Turnbull 2007).

Given the limited treatment options offered by conventional Western medicine, the lack of evidence of effectiveness and safety for those options, and the occurrence of side effects common to conventional medications, it is not surprising that sufferers of chronic fatigue use a range of CAM therapies (Afari 2003, Carruthers 2003, Jones 2007). CAM treatments that have been documented in ICF/CFS populations include massage, megavitamins and nutritional supplements, herbals, acupuncture, and homeopathy, however, supporting evidence for these therapies is also limited. Few clinical trials have been conducted for CAM therapies and those that have been published are contradictory, inconclusive, or have not yet been replicated (Afari 2003, Carruthers 2004, Porter 2010, Rimes 2005, Turnbull 2007).

1.2.2.4 Etiology of ICF/CFS

The etiology of ICF/CFS is as yet unexplained, although numerous risk factors have been proposed, including genetic disposition, physical or emotional stressors, and viral infection (Carruthers 2003, Fennel 2003, Lloyd 2003, Patarca-Montero 2004, Sullivan 2003, Turnbull 2007, Wessely 1999). Fatigue is a common symptom of viral infection although severity may vary according to parameters such as type of infection, initial health of the host, and treatment options employed. Explorations of the potential influence of viral infection have been conducted. One such virus is Epstein-Barr (EBV), whose symptomatic presentation as mono is often characterized by severe acute fatigue, and in some cases by prolonged or chronic fatigue. In a prospective cohort study examining the link between long-term fatigue and EBV, the authors followed a group with mono and a group with upper respiratory tract infections (UTRI). In those with mono, fatigue was present at two months and six months in 68% and 40%

respectively compared to 19% and 15% in those with URTI ($p<0.001$ and $p=0.007$ respectively) (White 1998). A more recent study examined the association between fatigue and infectious disease by comparing mono to two other viral conditions. The odds ratios for presence of clinical fatigue during the year following diagnosis with mono was 4.4 (95% CI 2.9-6.9, $p<0.0001$) in relation to influenza, and 6.6 (95% CI 4.2-10.4, $p<0.0001$) in relation to tonsillitis (Petersen 2006).

1.2.2.5 Epstein-Barr Viral Infectious Mononucleosis

EBV infection is ubiquitous in the general population and while most infection is asymptomatic, mono is the most common clinical manifestation. Although all ages may be infected, mono is most often experienced by adolescents and young adults (Johannsen 2005). The most common signs and symptoms of mono include fever, chills, severe sore throat, swollen glands, headaches, body aches, and fatigue (APHA 2000). For many, mono is a self-limited illness that lasts several weeks, however, cohort studies have reported fatigue lasting two months or more in up to 68% of patients followed (Rea 2001, White 1998).

1.2.2.6 Diagnosis of Infectious Mononucleosis

A diagnosis of mono is generally based on signs and symptoms as well as blood tests for characteristic antibodies such as heterophile antibodies and IgM to viral capsid antigens (VCA). While IgM VCA peaks early in the infection and persists for 4-8 weeks, heterophile antibodies can be detected indefinitely (Ebell 2004, Johannsen 2005). Heterophile antibody tests have reported sensitivity (ability to detect true presence of specified antibodies) ranging between 71-95% and specificity (ability to detect true absence of specified antibodies) ranging between 82-99%, while testing for IgM VCA has sensitivity ranging between 95-99% and specificity ranging between 89-99% (Ebell 2004). Mono is commonly diagnosed using the Monospot heterophile antibody test and has a reported sensitivity of 94% and specificity of 98% (Meridian Bioscience 2004).

1.2.2.7 Incidence and Burden of Infectious Mononucleosis

Incidence rates in community populations are not readily available since mono is not a reportable disease. Several studies looking at mono incidence have been published, but none in recent years. Three population studies in the UK and the US, published between 1958 and 1972, reported mono incidences ranging from 0.044% to 0.1% (Davidson 1970, Heath 1972, Hobson 1958), however, incidence in at risk populations, such as university students, have been reported to be much higher (i.e. >10%) (Niederman 1970, Sawyer 1971). Another study, in military populations, reported that mono ranked fourth in causes of days lost to illness, with a four-year incidence rate of 12% (Halle 1974). As part of this dissertation, local mono incidence will be determined (Chapter 4).

1.2.2.8 Treatment of Infectious Mononucleosis with Conventional Medicine

Although mono can be readily diagnosed through a physical exam and simple blood tests, there is no cure. Current treatment for uncomplicated mono is generally limited to symptom support such as rest, analgesics, anti-inflammatory medicine, and adequate hydration (Ebell 2004, Johannsen 2005). Examination of specific evidence has led to the recommendations that acyclovir and corticosteroids not be prescribed due to the lack of significant or consistent clinical benefit (Roy 2004, Torre 1999, Tynell 1996). One recent study that examined the advice that physicians give to patients with mono reported that the most common recommendation was to rest or take it easy (70%), followed by simple symptom management with over-the-counter drugs and fluids (17%), and diet modification (10%) (Candy 2005).

1.2.3 Fatigue in Traditional Chinese Medicine

Fatigue is a symptom that is characteristic of diagnoses involving Qi deficiency, for which the dominant treatment principle would be to tonify (increase or strengthen) Qi in the affected areas. Major acu-points recommended for this purpose include Stomach 36, Spleen 6, Governing Vessel 4 and 6, and

Urinary Bladder 20, as well as points specific to the affected organ system (Stux 1988).

Historical records document treatment of various forms of fatigue with TCM (Buchwald 1994, Cohen 2000). More recent accounts can be found in case reports, reviews, and clinical studies.

1.2.3.1 Treatment of Chronic Fatigue with Traditional Chinese Medicine

Successful treatment of chronic conditions is reputed to be a strength of TCM (Cohen 2000, Huizing 1995, McCulloch 2002). Descriptions of chronically fatiguing illnesses can be found in a TCM text that is 2000 years old (Buchwald 1994). More recently, textbooks used for TCM training outline conditions that include ICF and CFS and the methods used to treat them (Aung 2007, Becker 2000, Flaws 2001, Maciocia 1994, Maciocia 2004). Similarly, summary reports of treatment of chronic fatigue with TCM specifically describe common symptom patterns for CFIDS and CFS, and the corresponding approaches that are used to treat them (Chen 1999b, Vickers 1994). Medicinal herbs, diet therapy, moxibustion, and acupuncture are among the therapies described. A recent survey of the use of CAM by people with chronically fatiguing illnesses in the US reported that over 2% of those with chronic fatigue or CFS-like illness had used acupuncture in the previous year (Jones 2007).

Approaches for the treatment of CFS with acupuncture include choice of acu-points (which will vary somewhat based on specific patterns of symptoms). Examples of treatment recommendations include those of respected TCM teachers such as Dr. Aung and Dr. Maciocia (Aung 2007, Maciocia 1994). In his textbook Dr. Aung suggests that the treatment of CFS may include the following points, depending on specific presentation, Kidney 3 and 10, Liver 3, Spleen 8 and 9 as primary points; Bladder 18, 20 and 23, Conception Vessel 4, 5, 6, and 17, and Governing Vessel 4 as supportive secondary points; Liver 13, Conception Vessel 12, Spleen 21, and Large Intestine 11 as supplementary tertiary points; and Heart 7, Pericardium 6, Triple Energizer 5, Governing Vessel 20, and Extra Head/Neck 1 as special quaternary points. In cases of CFS presenting with Qi deficiency, Dr.

Maciocia recommends tonification of Qi in specific areas through the use of some or all of Stomach 36, Spleen 6, Bladder 20, 21, and 23, Lung 9, Heart 5, Large Intestine 10, and Governing Vessel 12 and 20.

Evidence for acupuncture treatment of fatigue conditions includes case reports and practice reviews (Chaudhuri 2008, Chen 1999b, Mears 2005, Vickers 1994), TCM textbooks (Becker 2000, Flaws 2001, Maciocia 1994, Scott 1999) and anecdotes, as well as observational studies and trials (Table 1.2) (Balk 2009, Buchwald 1991, Li 2006, Martin 2006, Molassiotis 2006, Vickers 2004, Wang 2001, Wang 2009, Yan 2003).

Table 1.2: Acupuncture Studies for Fatigue Outcomes

Author; Date	Design	Population	N	Control	Effect on fatigue
Buchwald; 1991	PCS	CFS	22	Not applicable	61 % of patients improved
Wang; 2001	CCT	CFS	50	Chinese herbal medicine	Improved over control ($p<0.05$)
Yan; 2003	PCS	CFS	38	Not applicable	Total effective rate 92%
Vickers; 2004	Phase II	Cancer, post-chemo	37	NA Not applicable	Reduction of 31%
Martin; 2006	RCT	FM	50	Non-penetrating sham*	Improved over control ($p<0.05$)
Li; 2006	CCT	CFS	64	Hydro-cortisone	Improved over control ($p<0.05$)
Molassiotis 2006	RCT	Cancer-related fatigue	47	Acupressure at same or different points (sham acupressure)	Improvement in 36% (acupuncture), 19% (acupressure), 0.6% (sham)
Balk; 2009	RCT pilot	Cancer-related fatigue	27	Park Sham Device (non-penetrating)	No significant difference
Wang; 2009	RCT**	CFS	70	Acupuncture at non-meridian points	Both groups improved significantly over baseline

N = sample size; PCS = prospective cohort study; RCT = randomized controlled clinical trial; CCT = controlled clinical trial; CFS = chronic fatigue syndrome; FM = fibromyalgia; * sham procedure included pressure and adhesion of needle handle at true points; **many Chinese RCTs have been shown to use improper methods, thus classification is noted with caution

1.2.3.2 Treatment of Infectious Mononucleosis with Traditional Chinese Medicine

The TCM characterization of EBV-mono includes the presence of a lingering pathogenic factor and descriptions of symptom patterns may indicate excess heat and deficiency of Qi (Becker 2000, Maciocia 1994, Scott 1999). Anecdotal evidence and textbook summaries suggest that TCM modalities may have some effect in reducing symptoms of mono and shortening recovery. Treatment principles that may be applied include enhancing the immune system, restoring balance, and strengthening Qi. Modalities that have been used in the treatment of mono include herbs and acupuncture (Becker 2000, Maciocia 1994, Scott 1999). While herbs are commonly part of treatment, acupuncture, without the use of herbs, is successfully practiced by some acupuncturists, especially in Western countries (personal communication).

Decisions that need to be made in the treatment of mono with acupuncture include choice of acu-points (which will vary somewhat based on specific patterns of symptoms). An example of an acupuncture treatment protocol can be found in a textbook focusing on the use of acupuncture in children (Scott 1999). The authors recommend that in the acute stage acupuncture be applied to order to clear heat, resolve toxicity, transform the phlegm, and disperse knots by using Large Intestine 4 and 11, and Governing Vessel 14. The authors make reference to addition of Triple Energizer (also called Triple Burner) 10 and 17, and Gall Bladder 21, however, they had not personally used these points. In the next stage, where fever is gone but other symptoms remain, the authors recommend the use of Bladder 18 and 20, Spleen 6, Liver 2, Large Intestine 11, Heart 3, Lung 9, Stomach 36, and Extra Head/Neck point 30.

Because of the scarcity of mono treatment guidelines, consultation with local TCM practitioners and educators was undertaken. These practitioners believed that the following points would be important to consider during treatment of EBV-mono: Spleen 6 and 10, Gall Bladder 20, Lung 11, Small Intestine 17, Large Intestine 4 and 11, Stomach 36, Conception Vessel 6 and 17, and Governing Vessel 14 (personal communication).

Despite the availability of treatment guides for mono, the state of the published literature on clinical research in this area is unknown. Clinical evidence for the efficacy of acupuncture has been reported in studies of other viral infections, including hepatitis (Chen 1999a), HIV (Anastasi 1993, Beal 2000, Chang 2007), and the common cold (Kawakita 2004). Outcomes from these trials commonly demonstrated enhancement of the immune system and symptom improvement, however, fatigue was not specifically measured (Table 1.3).

Table 1.3: Acupuncture Trials for Viral Infection

Author; Date	**Design**	**Population**	**N**	**Control**	**Effect**
Anastasi; 1993	PCS	HIV	15	Not applicable	Statistically significant decrease in diarrhea parameters
Chen; 1999	CCT	Hepatitis B	90	Dietary supplements	Statistically significant increase in immune function
Beal; 2000	RCT	HIV	11	Acupuncture at non-indicated points	No significant difference between groups; pooled data showed overall improvement in number of HIV symptoms (p=0.02) and physical well being (p=0.05).
Kawakita 2004	RCT	Common cold	326	No treatment	Significant reduction in symptoms (p=0.024)
Chang; 2007	RCT	HIV	119	Relaxation + acupuncture	Relaxation + acupuncture better in improving QoL than acupuncture alone

N = sample size; PCS = prospective cohort study; RCT = randomized controlled clinical trial; CCT = controlled clinical trial; HIV = Human Immunodeficiency Virus; QoL = quality of life

1.3 Specific Objectives

i) To examine the efficacy of TCM for two fatigue conditions through SRs of TCM for mono and chronic fatigue, and to conduct an RCT of acupuncture for mono;

ii) To examine the safety of pediatric acupuncture through an SR.

1.4 Organization of Dissertation

Chapter 2 presents two SRs of TCM, one for mono and one for chronic fatigue, followed by discussion of the methodological issues identified in these reviews; chapter 3 presents an SR of the safety of pediatric acupuncture; chapter 4 describes the protocol and results of an RCT of acupuncture for mono; and chapter 5 provides a summary and synthesis of the preceding chapters.

1.5 Reference List

Afari N, Buchwald D. Chronic fatigue syndrome: A review. *American Journal of Psychiatry.* 2003;160:221-236.

American Public Health Association. Infectious mononucleosis, In *Control of Communicable Diseases Manual*, 17th ed. J Chin, ed. Washington, DC: American Public Health Association, 2000 p351-352.

Anastasi J, McMahon D. Testing strategies to reduce diarrhea in persons with HIV using traditional Chinese medicine: acupuncture and moxibustion. *Journal of the Association of Nurses in AIDS Care.* 2003;14(3):28-40.

Aung SKH, Chen WPD. *Clinical Introduction to Medical Acupuncture*. New York, NY: Thieme Medical Publishers, Inc., 2007.

Balk J, Day R, Rosenzweig M, Beriwal S. Pilot randomized, modified, double-blind, placebo-controlled trial of acupuncture for cancer-related fatigue. *Journal for the Society of Integrative Oncology*. 2009;7(1):4-11.

Beal M, Nield-Anderson L. Acupuncture for symptom relief in HIV-positive adults: lessons learned from a pilot study. *Alternative Therapies in Health and Medicine.* 2000;6(5):33-42.

Barnes PM, Bloom B, Nahin RL. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. *National Health Statistics Reports*. 2008;12.

Becker S. *A Handbook of Chinese Hematology.* Boulder, CO: Blue Poppy Press, 2000 p132-135.

Berman B, Singh B, Lao L, Langenberg P, Li H, Hadhazy V et al. A randomized trial of acupuncture as an adjunctive therapy in osteoarthritis of the knee. *Rheumatology*. 1999;38:346-354.

Berman B, Swyers J, Ezzo J. The evidence for acupuncture as a treatment for rheumatologic conditions. *Rheumatic Diseases Clinics of North America*. 2000;26(1):103-115.

Bierl C, Nisenbaum R, Hoaglin D, Randall B, Jones A, Unger E et al. Regional distribution of fatiguing illnesses in the United States: a pilot study. *Population Health Metrics.* 2004;2:1.

Birch S. Clinical research on acupuncture: Part 1. What have reviews of the efficacy and safety of acupuncture told us so far? *Journal of Alternative and Complementary Medicine.* 2004;10(3):468-480.

Birch S. A review and analysis of placebo treatments, placebo effects, and placebo controls in trials of medical procedures when sham is not inert. *Journal of Alternative and Complementary Medicine*. 2006;12(3):303-310.

Bombardier C, Buchwald D. Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. *Medical Care.* 1996;34:924-930.

Borud E, Alraek T, White A, Fonnebo V, Eggen AE, Hammar M et al. The acupuncture on hot flushes among menopausal women (ACUFLASH) study, a randomized controlled study. *Menopause*. 2009;16(3):484-493.

Brinkhaus B, Witt C, Jena S, Liecker B, Wagscheider K, Willich SN. Acupuncture in patients with allergic rhinitis: a pragmatic randomized trial. *Annals of Allergy, Asthma & Immunology*. 2008;101:535-543.

British Medical Association (BMA). *Acupuncture: Efficacy, Safety and Practice*. Amsteldijk, The Netherlands: Harwood Academic Publishers, 2000.

Buchwald D. Defining chronic fatigue syndrome. In: Straus, S editor, *Chronic Fatigue Syndrome.* New York, NY: Marcel Dekker, Inc, 1994 p46.

Buchwald D, Blair J, Mease P. Treatment of chronic fatigue syndrome with acupuncture. International *Journal of Clinical Acupuncture.* 1991;2(3):231-236.

Buchwald D, Umali P, Umali J, Kith P, Pearlman T, Komaroff AL. Chronic fatigue and the chronic fatigue syndrome. Prevalence in a Pacific Northwest health care system. *Annals of Internal Medicine*. 1995;123(2):81-88.

Cairns R, Hotopt M, A systematic review describing the prognosis of chronic fatigue syndrome. *Occupational Medicine*. 2005;55(1):20-31.

Candy B, Chalder T, Cleare AJ, Wessely S, Hotopf M. What advice to patients with infectious mononucleosis report being given by their general practitioner? *Journal of Psychosomatic Research*. 2005;55:435-437.

Carruthers B, Jain A, De Meirleir K, Peterson D, Klimas N, Lerner A, Bested A et.al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *Journal of Chronic Fatigue Syndrome.* 2003;11:7-115.

Centers for Disease Control and Prevention (CDC). *Chronic Fatigue Syndrome.* 2009. www.cdc.gov/cfs/ (Accessed Aug 18, 2009).

Chang BH, Boehmer U, Zhao Y, Sommers E. The combined effectof relaxation response and acupuncture on quality of life in patients with HIV: a pilot study. *Journal of Complementary and Alternative Medicine*. 2007;13(8):807-815.

Chaudhuri G. Acupuncture treatment for an adolescent with chronic fatigue syndrome. *Medical Acupuncture.* 2008;20(1):61-62.

Chen J, Chen M, Wang Y. Effects of acupuncture on the immunological functions in hepatitis B virus carriers. *Journal of Traditional Chinese Medicine.* 1999;19(4):268-272.

Chen J, Yang W. Treatment of chronic fatigue syndrome with Chinese medicine. *Journal of Chronic Fatigue Syndrome.* 1999;5:61-65.

Cohen M, Gish R. *The Hepatitis C Help Book: A Groundbreaking Treatment Program Combining Western and Eastern Medicine for Maximum Wellness and Healing.* New York, NY: St. Martin's Press, 2000 p92-122.

Darbishire L, Ridsdale L, Seed PT. Distinguishing patients with chronic fatigue from those with chronic fatigue syndrome: a diagnostic study in UK primary care. *British Journal of General Practice*. 2003;53:441-445.

Davidson RJL. A survey of infectious mononucleosis in the North-East Regional Hospital Board area of Scotland 1960-9. *The Journal of Hygiene*. 1970;68:393-400.

De Meirleir K, McGrego, N. Chronic fatigue syndrome guidelines. *Journal of Chronic Fatigue Syndrome.* 2003;11:1-5.

Dincer F, Linde K. Sham interventions in randomized clinical trials of acupuncture – a review. *Complementary Therapies in Medicine.* 2003;11:235-242.

Ebell Mark. Epstein-Barr virus infectious mononucleosis. *American Family Physician.* 2004;70:1279-87, 1289-90.

Fennell PA. Sociocultural context and trauma. In: Jason LA, Fennell PA, Taylor RR editors, *Handbook of Chronic Fatigue Syndrome*. Hoboken, NJ: John Wiley & Sons, Inc. 2003 p73-88.

Flaws R. Traditional Chinese medicine. In: Burton Goldberg Group editors, *Alternative Medicine: The Definitive Guide*. Fife, WA: Future Medicine Publishing, 1993 p450-456.

Flaws R. *The Treatment of Modern Western Diseases with Chinese Medicine: A Textbook & Clinical Manual*. Boulder, Colorado: Blue Poppy Press, 2001 p141-145.

Halle TJ, Evans AS, Neiderman JC, Brooks CM, Voegtly JH. Infectious mononucleosis at the United States Military Academy. A prospective study of a single class over four years'. *Yale Journal of Biology and Medicine*. 1974;47(3):182-195.

Heath Jr CW, Brodsky AL, Potolsky AI. Infectious mononucleosis in a general population. *American Journal of Epidemiology*. 1972;95(1):46-52.

Hobson FG, Lawson B, Wigfield M. Glandular fever: a field study. *BMJ*. 1958;1(5075):845-852.

Huizing, A. *Acupuncture: An Introduction to Traditional Chinese Medicine.* Edmonton, AB: Angie Huizing Publishing, 1995:1-14.

Jason L, Richman J, Rademaker A, Jordan K, Plioplys A, Taylor R et.al. A community-based study of chronic fatigue syndrome. *Archives of Internal Medicine*. 1999;159:2129-2137.

Jindal V, Ge A, Mansky P. Safety and efficacy of acupuncture in children: a review of the evidence. *Journal of Pediatric Hematology/Oncology*. 2008;30(6):431-442.

Johannsen E, Schooley RT, Kaye K. Epstein-Barr virus (infectious mononucleosis), In Mandell, Douglas, and Bennett's *Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia, PA: Churchill Livingstone, 2005 p1801–1820.

Jones JF, Maloney EM, Boneva RS, Jones AB, Reeves WC. Complementary and alternative medical therapy utilization by people with chronically fatiguing illnesses in the United States. *BMC Complementary and Alternative Medicine*. 2007;7(12):doi:10.1186/1472-6882-7-12.

Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. *Quarterly Journal of Medicine*. 1997;90:223-233.

Kaptchuk T. Placebo needle for acupuncture (letter). *Lancet.* 1998;352:992.

Kaptchuk T. Acupuncture: theory, efficacy and practice. *Annals of Internal Medicine.* 2002;136:374-383.

Kaptchuk T, Stason W, Davis R, Legedza A, Schnyer R, Kerr C, Stone D, et.al. Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ.* 2006. doi:10.1136/bj.38726.603310.55

Kawakita Shichidou T, Inoue E, Nabeta T. Preventive and curative effects of acupuncture on the common cold: a mulitcentre randomized controlled trial in Japan. *Complementary Therapies in Medicine.* 2004;12:181-188.

Kleinhenz J, Streitberger K, Windeler J, Gubbacher A, Mavridis G, Martin E. Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendonitis. *Pain.* 1999;83:235-241.

Lao L, Bergman S, Hamilton G, Langenberg P, Berman B. Evaluation of acupuncture for pain control after oral surgery. *Archives of Otolaryngology and Head and Neck Surgery.* 1999;125:567-572.

Lee GBW, Charn TC, Chew ZH, Ng TP. Complementary and alternative medicine use in patients with chronic diseases in primary care is associated with perceived quality of care and cultural beliefs. *Family Practice.* 2004; 21: 654–660.

Leggett Tait, P, Brooks L, Harstall C. *Acupuncture: Evidence from Systematic Reviews and Meta-Analyses*. Edmonton, Alberta: Alberta Heritage Foundation for Medical Research Publishing, 2002.

Levine P, Schwartz S, Furst G. Medical intervention and management. In: Jason LA, Fennell PA, Taylor RR editors, *Handbook of Chronic Fatigue Syndrome*.

Hoboken, NJ: John Wiley & Sons, Inc. 2003 p441-454.
Lewith G, Machin D. On the evaluation of the clinical effects of acupuncture. *Pain.* 1983;16:111-127.

Li Y, Liu H, Shulan F, Dongfang G. The therapeutic effects of electrical acupuncture and auricular plaster in 32 cases of chronic fatigue syndrome. *Journal of Traditional Chinese Medicine.* 2006;26(3):163-164.

Lloyd A. Postinfective fatigue. In: Jason LA, Fennell PA, Taylor RR editors, *Handbook of Chronic Fatigue Syndrome*. Hoboken, NJ: John Wiley & Sons, Inc. 2003 p108-123.

Maciocia G. *The Foundations of Chinese Medicine.* New York, NY: Churchill Livingstone Inc., 1989.

Maciocia G. *The Practice of Chinese Medicine.* New York, NY: Churchill Livingstone Inc., 1994 p315-357, 631-655.

Maciocia G. *Diagnosis in Chinese Medicine: a comprehensive guide.* New York, NY: Churchill Livingstone Inc., 2004 p974-979.

Martin D, Sletten C, Williams B, Berger I. Improvement in fibromyalgia symptoms with acupuncture: results of a randomized controlled trial. *Mayo Clinic Proceedings*. 2006;81(6):749-757.

Mayer D. Acupuncture: an evidence-based review of the clinical literature. *Annual Reviews in Medicine.* 2000;51:49-63.

McCrone P, Darbishire L, Ridsdale L, Seed P. The economic cost of chronic fatigue and chronic fatigue syndrome in UK primary care. *Psychological Medicine*. 2003;33:253-261.

McCulloch M, Broffman M, Gao J, Colford Jr J. Chinese herbal medicine and interferon in the treatment of chronic hepatitis B: A meta-analysis of randomized, controlled trials. *American Journal of Public Health*. 2002;92:1619-1627.

Mears T. Acupuncture in the treatment ofpost viral fatigue syndrome – a case report. *Acupuncture in Medicine.* 2005;23(3):141-145.

Melchart D, Streng A, Hope A, Brinkhaus B, Witt C, Wagenpfeil S et al. Acupuncture in patients with tension-type headache: a randomised controlled trial. *BMJ*. 2005;doi:10.1136/bmj.38512.405440.8F.

Melchart D, Weidenhammer W, Streng A, Reitmayr S, Hoppe A, Ernst E, Linde K. Prospective investigation of adverse effects of acupuncture in 97 733 patients. *Archives of Internal Medicine.* 2004;164:104-105.

Meridian Bioscience Europe. *Monospot*. Cincinnati, OH: Meridian Bioscience, Inc. 2004.

Molassiotis A, Sylt P, Diggins H. The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure: a randomized controlled trial. *Complementary Therapies in Medicine*. 2007;15:228-237.

National Institutes of Health (NIH). *NIH Consensus Statement: Acupuncture.* 1997. www.consensus.nih.gov/1997/1997Acupuncture107html.htm (Accessed Sept 15, 2009).

Niederman J, Evans A, Subrahmanyan L, McCollum R. Prevalence, incidence and persistence of EB Virus antibody in young adults. *New England Journal of Medicine*. 1970;282(7):361-365.

Park J. Use of Alternative Health Care. *Health Reports.* 2004;16(2):39-42.

Park J, White A, James M, Hemsley A, Johnson P, Chambers J, Ernst E. Acupuncture for subacute stroke rehabilitation. *Archives of Internal Medicine.* 2005;165:2026-2031.

Park J, White A, Stevinson C, Ernst E, James, M. Validating a new non-penetrating sham acupuncture device: two randomized controlled trials. *Acupuncture in Medicine.* 2002;20(4):168-174.

Park J, Linde K, Manheimer E, Molsberger A, Sherman K, Smith C, Sung J, Vickers A, Schnyer R. The status and future of acupuncture research. *Journal of Alternative & Complementary Medicine.* 2008;14(7): 871-881.

Patarca-Montero R. *Medical Etiology, Assessment, and Treatment of Chronic Fatigue and Malaise*. Binghamton, NY: The Hawthorn Medical Press, 2004 p1-19, 121-229.

Paterson C, Britten N. Acupuncture as a complex intervention: a holistic model. *Journal of Alternative and Complementary Medicine.* 2004;10(5):791-801.

Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. *BMJ.* 2005;330:1202-1205.

Petersen I, Thomas JM, Hamilton WT, White PD. Risk and predictors of fatigue after infectious mononucleosis in a large primary cohort. *Quarterly Journal of Medicine*. 2006;99:49-55.

Porter NS, Jason LA, Boulton A, Bothne N, Coleman B. Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. *Journal of Alternative and Complementary Medicine*. 2010;16(3):235-249.

Ranjith G. Epidemiology of chronic fatigue syndrome. *Occupational Medicine*. 2005;55(1):13-19.

Rea T, Russo J, Katon W, Ashley R, Buchwald D. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr Virus. *Journal of the American Board of Family Practice.* 2001;14:234-242.

Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The economic impact of chronic fatigue syndrome. *Cost Effectiveness and Resource Allocation*. 2004;2:4 doi:10.1186/1478-7547-2-4.

Rimes KA, Chalder T. Treatments for chronic fatigue syndrome. *Occupational Medicine*. 2005;55(1):32-39.

Rosenberg EI. Genao I, Chen I, Mechaber AJ, Wood JA, Faselis CJ et al. Complementary and alternative medicine use by primary care patients with chronic pain. *Pain Medicine*. 2008;9(8):1065-1072.

Roy M, Bailey B, Amre DK, Girodias JB, Bussières JF, Gaudreault P. Dexamethasone for the treatment of sore throat in children with suspected IM. *Archives of Pediatric and Adolescent Medicine*. 2004;158(3):250-254.

Salter GC, Roman M, Bland MJ, MacPherson H. Acupuncture for chronic neck pain: a pilot randomised controlled trial. *BMC Musculoskeletal Disorders*. 2006;7:99. doi:10.1186/1471-2474-7-99.

Sanchez Araujo, M. Does the choice of placebo determine the results of clinical studies on acupuncture? *Forschende Komplementarmedizin.* 1998;5(suppl 1):8-11.

Sawyer RN, Evans AS, Niederman JC, McCollum RW. Prospective studies of a group of Yale university freshmen. Occurrence of infectious mononucleosis. *Journal of Infectious Diseases*. 1971;123(3):263-270.

Schneider A, Enck P, Streitberger K, Weiland C, Bagheri S, Witte S et al. Acupuncture treatment in irritable bowel syndrome. *Gut*. 2006;55:649-654.

Scott J. *Acupuncture in the Treatment of Children,* 3rd Ed. Seattle, WA: Eastland Press Inc, 1999 p520-529.

Skapinakis P, Lewis G, Mavreas V. One-year outcome of unexplained fatigue syndromes in primary care: results from an international study. *Psychological Medicine*. 2003;33:857-866.

Skapinakis P, Lewis G, Meltzer H. Clarifying the relationship between unexplained chronic fatigue and psychiatric morbidity: results from a community survey in Great Britain. *American Journal of Psychiatry*. 2000;157(9):1492-1498.

Smith P, Mosscrop D, Davies S, Sloan P, Al-Ani Z. The efficacy of acupuncture in the treatment of tempromandibular joint myofascial pain: a randomized controlled trial. *Journal of Dentistry.* 2007;35:259-267.

Streitberger K, Kleinhenz, J. Introducing a placebo needle into acupuncture research. *Lancet*. 1998;352:364-365.

Streitberger K, Vicker A. Placebo in acupuncture trials. *Pain*. 2004;109:195.

Stux G, Berman B, Pomeranz B. *Basics of Acupuncture,* 5th Ed. Berlin, Germany: Springer-Verlag. 1988.

Sullivan PF. Genetics. In: Jason LA, Fennell PA, Taylor RR editors, *Handbook of Chronic Fatigue Syndrome*. Hoboken, NJ: John Wiley & Sons, Inc. 2003 p89-107.

Taylor RR, Jason LA, Richman JA, Torres-Harding SR, King C, Song S. Epidemiology. In: Jason LA, Fennell PA, Taylor RR editors, *Handbook of Chronic Fatigue Syndrome*. Hoboken, NJ: John Wiley & Sons, Inc. 2003 p3-25.

Thomas K, MacPherson H, Thorpe L, Brazier J, Fitter M, Campbell M, Roman M et al. Randomized controlled trial of a short course of traditional acupuncture compared with usual care for persistent non-specific low back pain. *BMJ.* 2006;333(623):dol:10.1136/bmj.38878.907361.7C.

Tough E, White A, Richards S, Lord B, Campbell J. Developing and validating a sham acupuncture needle. *Acupuncture in Medicine*. 2009;27(3):118-122.

Torre D, Tambini R. Acyclovir for treatment of IM: a meta-analysis. *Scandinavian Journal of Infectious Diseases*. 1999;31(6):543-547.

Turnbull N, Shaw EJ, Baker R, Dunsdon S, Costin N, Britton G, Kuntze S and Norman R. *Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy): Diagnosis and Management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy) in Adults and Children*. London, UK: Royal College of General Practitioners, 2007.

Tynell E, Aurelius E, Brandell A, Julander I, Wood M, Yao QY et al. Acyclovir and prednisolone treatment of AIM: a multicenter, double blind, placebo controlled study. *Journal of Infectious Disease*s. 1996;174(2):324-331.

Vickers A. Placebo controls in randomized trials of acupuncture. *Evaluation & The Health Professions.* 2002;25(4):421-435.

Vickers A, Straus D, Bearon B, Cassileth B. Acupuncture for postchemotherapy fatigue: a phase II study. *Journal of Clinical Oncology.* 2004;22(9):1731-1735.

Vickers E, Dharmananda S, Fruehauf H. Treatment of chronic fatigue immune deficiency syndrome with Chinese medicine. *International Journal of Oriental Medicine.* 1994;19:143-159.

Wang JJ, Song YJ, Wu ZC, Chu XO, Wang XJ, Wei LN et al. Randomized controlled clinical trials of acupuncture treatment of chronic fatigue syndrome. *Zhen Ci Yan Jiu*. 2009;34(2):120-124.

Wang W, Wu S. Clinical analysis on treatment of chronic fatigue syndrome with combination acupuncture with cupping. *Chinese Acupuncture and Moxibustion.* 2001;8:481-482.

Wessely S, Chalder T, Hirsch S, Wallace P, Wright D. The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. *American Journal of Public Health.* 1997;87:1449-1455.

Wessely S, Hotopf M, Sharpe M. *Chronic Fatigue and its Syndromes*. Oxford, UK: Oxford University Press, 1999 p30-32, 176-219.

White A. A cumulative review of the range and incidence of significant adverse events associated with acupuncture. *Acupuncture in Medicine.* 2004;22(3):122-133.

White A, Filshie J, Cummings T. Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complementary Therapies in Medicine.* 2001;9:237-245.

White P, Lewith G. Could neuroimaging help us to interpret the clinical effects of acupuncture? *Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschultz.* 2006;49:743-748.

White P, Thomas J, Amess J, Crawford D, Grover S, Kangro H, Clare A. Incidence, risk and prognosis of acute and chronic fatigue syndromes and psychiatric disorders after glandular fever. *British Journal of Psychiatry.* 1998;173:475-481.

World Health Organization (WHO). *Acupuncture: Review and Analysis of Reports on Controlled Clinical Trials*. Geneva, Switzerland: World Health Organization Publishing, 2002.

World Health Organization (WHO). *Traditional Medicine Strategy 2002–2005*. Geneva, Switzerland: World Health Organization Publishing, 2002.

Yamashita H, Tsukayama H. Safety of acupuncture practice in Japan: patient reactions, therapist negligence and error reduction strategies. *eCAM*. 2008;5(4):391-398.

Yamashita H, Tsukayama H, Tanno Y, Nishijo K. Adverse events in acupuncture and moxibustion treatment: a six-year survey at a national clinic in Japan. *Journal of Alternative and Complementary Medicine*. 1999;5(3):229-236.

Yamashita H, Tsukayama H, Tanno Y, Nishijo K. Adverse events related to acupuncture. *Journal of the American Medicine Association*. 1998;280:1563-1564,.

Yan H, Li Z. Clinical study on treatment of chronic fatigue syndrome with acupuncture and moxibustion based on differentiation of syndromes. *Chinese Acupuncture and Moxibustion.* 2003;23(4):197-199.

York University Centre for Health Studies. *Complementary and Alternative Practices and Therapies – A Canadian Overview.* Toronto, ON: York University Press, 1999.

Zhu X, Carlton AL, Bensoussan A. Development in and Challenge for Traditional Chinese Medicine in Australia. *Journal of Alternative and Complementary Medicine*. 2009;15(6):685–688.

Chapter 2: Systematic Reviews of Traditional Chinese Medicine Trials: How Does Language of Publication Affect Risk of Bias?

2.1 Introduction

Systematic reviews (SRs) are an important tool for the synthesis of research results and are used to guide both further research and clinical practice. As such, the accuracy of SR summaries is crucial. Limitation of bias is an important step in increasing accuracy and has been the focus of much research and discussion (Egger 1998, Egger 2001, Shekelle 2005). One potential source of bias in SRs is that of language of publication of included studies.

In an examination of the effect of excluding randomized controlled trials (RCTs) based on language of publication, Moher et al. determined that, for 79 meta-analyses of conventional medical treatments, the estimate of treatment effect did not differ depending on whether RCTs published in languages other than English (LOE) were included or not. The authors concluded that there was no evidence that excluding LOE RCTs led to biased estimates of intervention effect (Moher 2000). In a follow up study, however, Pham et al. extended this investigation to determine if this result held up when the interventions were from complementary and alternative medicine (CAM) rather than from conventional medicine (Pham 2005). This study showed that for CAM interventions, the estimates of effect differed depending on whether LOE RCTs were included or not, showing an average decrease of 63% when LOE RCTs were excluded. This result was not felt to be influenced by either publication bias or statistical heterogeneity. In their conclusions, the authors recommended that LOE RCTs of CAM interventions be routinely included in SRs.

Limiting bias in the conduct and reporting of studies has been shown to be important in increasing the accuracy of results (Balk 2002, Benson 2000, Chalmers 1983, Ioannidis 2001, Juni 2002, Khan 1996, Kunz 1998, Schulz 1995), and CAM studies are no exception. Attempts to document the quality of CAM studies, including RCTs, have been made (Bausell 2004, Moher 1996, Moher 2002,Pham 2005) and results have shown that although problems with the quality

of reporting of CAM RCTs were identified (Moher 2002), the overall quality of reporting was equal to or better than that of non-CAM RCTs (Pham 2005). Similar assessments have been carried out for LOE studies. Moher et al. showed that completeness of reporting of RCTs did not differ significantly between RCTs published in English and those published in French, German, Italian, and Spanish (Moher 1996). A review examining RCTs of traditional Chinese medicine (TCM), published in China, identified a number of methodological problems within this body of evidence (Tang 1999). Data on methodological quality were extracted and summarized from nearly 3000 RCTs that were identified from a random sample of Chinese TCM journals. Common problems that were described included inappropriate description of randomization method, absence of blinding, small sample sizes, use of another untested TCM intervention as a control, focus on short-term or intermediate-term outcomes, lack of reporting on baseline characteristics, compliance, completeness of follow-up, and adverse events, rare quantitative expression of outcomes, absence of intention-to-treat analyses, test intervention claimed to be effective in most studies, and publication as short reports. Authors of the RCTs included in this study were not contacted, thus the results of this study are reflective of reporting practices but may not be reflective of actual trial conduct.

Standard SR methodology has been to accept at face value the details contained in publications and to incorporate studies believed to meet inclusion criteria accordingly, in order to produce summaries. We are only aware of two studies that attempted to verify the methods reported in the studies that met or seemed to meet their inclusion criteria. In the first, Manheimer et al. surveyed authors of 51 English-language acupuncture RCTs about their methods. Although survey responses generally confirmed the reported methods, problems identified in 35 studies indicated that 14% did not use adequate methods to generate allocation sequences (Manheimer 2006). In the second study, Wu et al. used the Chinese-language database China National Knowledge Infrastructure to identify 3137 publications that claimed to be RCTs, of both TCM and conventional medical interventions (Wu 2009). Following interviews of study authors

regarding randomization methods and related quality features of their trials, only 207 studies (6.8%, 95% CI 5.9-7.7) were determined to be 'true' RCTs. In order to be judged as 'true' the following criteria had to be met: randomization sequence generated by random number table, calculator, or computer program, concealed coin toss, or concealed drawing of straws; studies performing allocation based on birth date, order of appearance, and patient wishes were ineligible. No statistically significant differences between TCM and conventional medical interventions were found. The most common reason noted for the discrepancy between 'claimed' and 'true' RCTs was lack of knowledge and understanding about trial design, including randomization theory and practice, by study investigators and authors. Wu et al. concluded that false RCTs contaminate Chinese medical information, that researchers have wasted time and money producing low quality material, and that this material introduces risk of misleading healthcare providers, consumers, and policy makers. They advise SR authors that inclusion of Chinese RCTs simply based on claims of randomization are insufficient and that verification of study methods by author interview is warranted (Wu 2009). Although the scope of the study is too small and focused to generalize the findings it is suggestive of a larger problem. In both examples, the identified studies would have been more appropriately labelled as controlled clinical trials (CCTs) than RCTs, a distinction that may have affected their inclusion in an SR of RCTs.

TCM therapies, such as acupuncture and herbal medicine, are commonly used, not only in Asia, where TCM has a long history, but increasingly in the West (Barnes 2008, Statistics Canada 2004, WHO 2002, York University 1999). The conduct of SRs of TCM therapies is important in determining the current state of clinical evidence.

The purpose of this study was three-fold: i) to assess the efficacy and safety of TCM in treating fatigue related to EBV-infectious mononucleosis (mono) or idiopathic chronic fatigue (ICF), ii) to determine the value of adding Chinese-language databases to conventional search strategies of English-language

databases, and iii) to determine the importance of methodological validation of TCM RCTs in the conduct of two health conditions, mono and ICF.

2.2 Methods

The methods used for two SRs were very similar and will be presented together; differences will be highlighted.

Types of studies

Randomized controlled trials

Types of participants

Participants were not restricted by gender, age or ethnicity. ***Mono SR*** Participants must have been diagnosed with EBV-mono. ***ICF SR*** Participants must have been diagnosed with chronic fatigue of unknown etiology, lasting at least 6 months, according to accepted diagnostic guidelines (i.e. Fukuda 1994, Holmes 1988, Lloyd 1990, Sharpe 1991).

Types of interventions

Therapies utilized in TCM, including but not limited to any one or combination of the following: herbs, acu-point stimulation, Qi-therapy, tui-na massage, cupping, dietary and lifestyle recommendations, and therapeutic exercise. Evaluation of participants and/or details of the intervention must have been applied according to TCM theory and practice.

Types of controls

Control groups may have consisted of placebo/sham TCM, active controls previously shown to be effective for EBV-mono or ICF, standard of care (SOC), or no treatment/wait lists; comparison of one intervention with another unproven intervention was not be accepted.

Types of outcome measures

Primary:

Fatigue (e.g. change in severity from baseline, comparison between treatment and control) as measured by a standardized or validated measurement tool (i.e. Fatigue Severity Scale, Chalder Fatigue Scale)

Secondary:

Change in related signs and symptoms, quality of life, global improvement, symptom impact (e.g. employment status), resource use (e.g. physician visits, medication use), cost analysis, and adverse events.

Search strategy

The following databases were searched for the indicated time periods or as far back as the databases go; the searches were not limited by language or publication status. MEDLINE (1966-2008), the Cochrane Central Register of Controlled Trials (CENTRAL Issue 2 2008), EMBASE (1980-2008), AMED (1985-2008), CINAHL (1982-2008), PSYCHINFO (1985-2008), the Chalmers Research Group PedCAM Database (2004), VIP Information (1989-2008), and China National Knowledge Infrastructure (CNKI 1976-2008). Additional material was also searched through Ovid's OCLC (Online Computer Library Center Inc (1992-2008), Conference Papers Index (1982-2008) and Dissertation Abstracts (1980-2008). Ongoing trials were sought through the Current Controlled Trials, National Institute of Health, National Research registers, and the Chinese Clinical Trial Registry (ChiCTR).

Search Strategies included terms for: i) randomized and/or controlled trials, ii) traditional Chinese medicine interventions, and iii) EBV, infectious mononucleosis, or glandular fever (***mono SR***) or fatigue (***ICF SR***). Full details of the search terms used are presented in appendices 1 and 2, respectively.

Selection of studies

Titles and abstracts of identified studies were independently screened by two reviewers. Full texts for potentially relevant studies were obtained and

reviewed for inclusion based on the following predetermined criteria: 1) described as an RCT; 2) population diagnosed with EBV-mono or ICF; 3) utilized TCM intervention; 4) control was placebo, sham, active control shown to be effective against EBV-IM or ICF, SOC, wait list, or no-treatment; and 5) reported on fatigue outcome.

In accordance with methodology employed by the Chinese Cochrane Centre in Chengdu, China, authors of studies identified through searches of the Chinese-language databases, that were described as randomized, were contacted by phone and interviewed about how patients were allocated to study groups, in order to verify that randomization was used. Studies where methods were not able to be verified were excluded (Wu 2009). Disagreement between reviewers was resolved by discussion.

Assessment of methodological quality

Methodological quality was independently assessed by two reviewers. The validated Jadad 5-point scale was used to assess randomization, blinding, withdrawals, and dropouts (Jadad 1998). Allocation concealment was assessed as adequate, inadequate, or unclear (Schulz 1995).

Planned data extraction

Data was extracted by one reviewer using standardized forms and verified by a second reviewer. Disagreement between reviewers was resolved by discussion. The following information was extracted: author; year, country and language of publication; funding source; objectives; study design; participant characteristics including age, gender, and ethnicity; diagnostic methods; number of participants who were eligible, enrolled and completed the study; diagnostic criteria and procedures; presence of intention-to-treat analysis; presence and method of randomization, blinding and allocation concealment; numbers and reasons for withdrawals and dropouts; details of TCM and SOC treatments including number and length of treatments; type of placebo/sham; qualifications of practitioners; presence of co-morbid disorders or concurrent medication; details

of each outcome measured as well as assessment tool(s) and assessor(s); measure of treatment effect; measure of compliance; and adverse events. If necessary, principle authors were contacted for further details.

Planned data synthesis

Data from multiple studies was analyzed using Review Manager Software. Analyses included stratification according to intervention/comparison (e.g. acupuncture vs. sham acupuncture, acupuncture vs. SOC, and acupuncture vs. no treatment) as outlined in the 'types of interventions' section. Dichotomous data was presented as relative risk (of improvement); continuous data was presented as weighted mean differences (for common measurement units) or standardized mean differences (for differing measurement units and different scales), along with corresponding 95% confidence intervals. The number needed to treat (for improvement) and number needed to harm (for adverse events) were determined for statistically significant outcomes. Heterogeneity was quantified with the I^2 statistic (Higgins 2003). If appropriate, subgroup analyses were carried out on the following categories: gender, age (i.e. pediatric vs. adult), baseline fatigue severity, intervention, and study quality score, for both, as well as subtype of chronic fatigue, diagnostic or inclusion criteria, and assessment tool (for the ICF SR). In order to control for attrition bias, intention to treat principles were applied. Publication bias was assessed visually using funnel plots and quantitatively assessed using weighted regression (Egger 1997).

2.3 Results

Mono SR

Searches of trial registries showed that there were no ongoing trials in this area other than that of Ms. Adams (Chapter 4), as of June 2008.

Searches of English-language databases retrieved 41 references but all were excluded during initial screening. Chinese-language database searches retrieved 2608 references. Screening of titles and abstracts reduced this number to 56, which were then obtained and assessed for inclusion; 42 were not labelled as

RCTs and were excluded. The remaining 14 studies, labelled as RCTs, were assessed by author interview, which determined that 10 of these were clinical experience summaries describing the effects of different TCM herbal treatments as well as the effects of conventional medicine, including antivirals (Chen 2005, Chen 2006, Liu 2007, Mo 2007, Sun 2006, Yan 2000, Yan 2006, Yang 2007a, Yang 2007b, Zen 2005), one was a quasi-randomized trial comparing herbs to Western medicine antivirals (Zhang 2006), and for 3 studies, the authors were unable to be contacted. For these studies, herbs were compared to conventional care, including antiviral drugs (Wang 2000, Wang 2006, Zhang 2000). According to standard SR methodology at the Chinese Cochrane Center, the unverified studies were excluded (Wu 2009).

ICF SR

Searches of trial registries showed that there were no ongoing trials in this area, as of June 2008.

Searches of English-language databases resulted in a total of 1324 references. Removal of duplicates reduces this number to 1004. Addition of Chinese-language database searches, conducted by our colleagues in Cheng Du China, added 1480 references, for a grand total of 2484 references. Screening of titles and abstracts excluded most references – 36 full articles were retrieved and assessed but all were excluded. Reasons for exclusion included: not an intervention study (4) (de Ruyter 1995, de Sylva 1992, Hill 1994, Sierpina 2002), use of quasi-randomization (1) (Yui 2007), not an ICF or CFS population (1) (Chen 2003), and use of invalid controls (30) (comparison of two TCM therapies (13) (Feng 2005; Jiao 2006; Lijue 2005; Liu 2006; Lu 2001; Luo 2006; Ni 2002; Shi 2004; Sun 2005; Wang 2004; Wang 2006; Xiong 2000; Yuan 2006) or a TCM therapy to a conventional care treatment not proven effective in ICF by clinical trial, including ATP, vitamins, amino acids, SSRIs, insulin, and cortisone (17) (Guo 2004, Kang 2006, Li 2005, Liang 2006, Meng 2006; Ning 2002; Pan 2005, Peng 2000; Pu 2002; Shu 1997; Tian 2006, Wei 2005, Yang 2004, Yao 2005, Zhang 2004a; Zhang 2004b, Zhao 2006)).

Of note, during the process of this review, 16 studies described as RCTs were subject to author interviews in order to verify randomization methods. Only two of the studies used acceptable randomization methods to assign participants to study groups, five used order of enrolment, six allowed the subjects to choose, and three used non-randomized study designs.

2.4 Discussion

CAM is popular and with increasing use the need for evidence summaries of both efficacy and safety also grows. Some forms of CAM, such as Ayurveda and TCM, developed within specific non-English cultures and it follows then that information about these practices may exist in material written and published in their respective languages. When conducting a literature review of a CAM therapy that is based in a particular culture, it seems logical to make every attempt to include evidence based in that culture and language. Taking the example of a SR of TCM, placing restrictions or limits on inclusion of studies, such as indexing in mainstream databases, indexing in English-language databases, or publication in English, do not seem to make sense. Closer examination of the contributions of TCM studies, however, introduces questions that make these decisions less straightforward.

TCM research is carried out both in China and in Western countries, with resultant publications in both Chinese and English. SR methods commonly recommend use of standard English-language databases such as MEDLINE and EMBASE (Lefebvre 2001), however, most of the journals in these databases are written in English (87.5% and 71.4%, respectively). Coverage of other languages is much more limited, with Chinese-language journals making up less than 2% of the total number of journals in each database (Pilkington 2005). Recent reports demonstrate that less than 5% of the more than 5000 journals published in Mainland China are indexed in standard English-language databases (Fung 2008, Xia 2008). Of the approximately 1300 Chinese biomedical journals, 149 publish TCM literature, four in English (Fan 2008). The authors also showed that only ten of these TCM journals were indexed in any of the following databases: PubMed,

EMBASE, AMED, or Biological Databases. In order to make up for this deficiency, databases that specifically publish LOE articles may need to be included.

Inclusion of LOE databases

In order to increase the coverage of Chinese-language publications, Chinese-language databases may be included in SR searches. Merits of conducting searches of Chinese-language databases include directedness and inclusiveness of search, however, this presents a number of logistical problems for authors not based in China, such as how to identify, select, and access databases, translation of terms (as some concepts may not be directly translatable), the need for personnel who read Chinese to search and manage materials, and related costs. One solution to these issues is to partner with a group that already has these resources.

During the conduct of the two SRs of mono and chronic fatigue previously described, we investigated the added value of including Chinese-language databases. After attempting to address the logistical problems listed previously we partnered with the Chinese Cochrane Center. Utilization of Chinese-language databases increased the number of potentially relevant references from 0 to 14 for the mono SR and from 8 to 36 for the chronic fatigue SR. Unfortunately, due to methodological limitations in the identified papers, the information gained from the extra searches did not generate any usable information.

Inclusion of LOE RCTs

The problems identified in the Chinese medical literature by Wu et al. raise very real concerns about the value of including Chinese RCTs in SRs. Techniques intended to reduce the potential for bias introduced by including studies that misuse the term ‘randomized’ may include routine verification of randomization methods, and in cases where verification is not possible, exclusion of these studies or reclassification as CCTs. An important issue raised by this research is that the assumptions made by SR authors, regarding the validity of

information provided in publications, including those of RCTs, may be flawed. These assumptions should be reconsidered in light of projects such as those by Manheimer et al. and Wu et al. (Manheimer 2006, Wu 2009).

Potential obstacles to routinely including methods verification of studies in SRs include language barriers in communicating with authors and increased time and cost to produce each SR.

The study by Wu et al. provides convincing values for the misrepresentation of RCTs in the Chinese medical literature. Similar large-scale studies in other languages, including English, may shed further light on the extent of this problem. Quantification of the bias introduced into SRs by inclusion of these studies would also be informative.

In light of the problems inherent in many Chinese RCTs, SR authors must determine the relative need for and potential value of including this material. For example, during the conduct of our two SRs 13 English-language databases were searched. When searches of these databases failed to identify any 'real' RCTs searches of two Chinese-language databases were initiated; unfortunately these searches also failed to identify any 'real' RCTs. These additional searches and subsequent SR steps represented substantial contributions in time and resources and yet did not increase our yield.

Improvements in conduct and reporting of studies would be the ideal way to avoid introducing bias into SRs due to poor quality or misrepresented studies. There are currently many initiatives that attempt to do just this, such as use of trial registries and reporting guidelines, such as CONSORT (Moher 2001). Restriction of publication to registered RCTs that follow CONSORT guidelines reinforces their use. Newer initiatives are also underway, such as those promoted by the Chinese Evidence-Based-Medicine Center (Li 2009). These include enhancing transparency of clinical trials through a clinical trial registry established in 2004 and a real time database to monitor trial conduct, use of standardized reporting based on CONSORT, establishing reliable quality control systems for medical research, and reinforcing education and clinical trial skills.

2.5 Conclusions

Published reports of verified RCTs of TCM for EBV-mono are not available. Searches of standard English-language databases did not identify any relevant RCTs, or, for that matter, studies of any other design, for any TCM therapy. Searches of Chinese-language databases identified publications labelled as RCTs, however, investigation revealed that these studies were misrepresented. There is currently no RCT evidence, as defined by this review, to support or refute the use of TCM for EBV-mono. Clinical studies of TCM for chronic fatigue syndrome are being conducted, however, methodological limitations, including lack of randomization, resulted in exclusion of all studies from the SR. The published literature around the use of TCM therapies to treat ICF does not currently contain convincing RCT evidence, as defined by this review. In order to be truly informative to practice, the bodies of evidence for both mono and chronic fatigue need to contain rigorously designed and conducted trials that include comparison either to a proven active control or, where one doesn't exist, to placebo or no treatment groups.

Previous work has demonstrated the importance of including foreign language CAM RCTs in SRs, with respect to estimates of effect. This study extends this point by examining the value of Chinese language RCTs and shows that upon closer examination most of the 'reported' RCTs are not in fact RCTs and thus should not be included in these estimates. Inclusion of Chinese RCTs, and possibly those in other languages, may add bias to a SR rather than reduce it.

It is hoped that current and future initiatives will reduce the problems outlined in this paper, however, the problems evident in past RCTs poses problems for current SR authors seeking to use this information. Given the finding of these SRs and the work conducted by Wu et al. that demonstrated that this problem exists across many medical conditions and interventions, we recommend caution in the use of current Chinese-language RCTs and potentially for those in other languages.

Endnotes

A version of this chapter has been published. Adams D, Wu T, Yang X, Tai S, Vohra S. Traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and chronic fatigue syndrome. *The Cochrane Library*, Issue 4 2009.

2.6 Reference List

Balk E, Bonis P, Moskowitz H, Schmid C, Ioannidis J, Wang C, Lau J. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *Journal of the American Medical Association.* 2002;287:2973-82.

Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *National Health Statistics Reports*. 2008;12.

Bausell R, Lee WL, Soeken K, Li YF, Berman B. Larger effect sizes were associated with higher quality ratings in complementary and alternative medicine randomized controlled trials. *Journal of Clinical Epidemiology.* 2004;57:438-446.

Benson K, Hartz A. A comparison of observational studies and randomized, controlled trials. *New England Journal of Medicine.* 2000;342:1878-86.

Chalmers T, Celano P, Sacks H, Smith H. Bias in treatment assignment in controlled clinical
trials. *New England Journal of Medicine.* 1983;309:1358-61.

Chen AM. Variable Shenjiangshan in the treatment of 30 children with infectious mononucleosis. *New Journal of TCM*. 2006;38(10):74-75.

Chen W. Clinical application of double-hand needling manipulation. *Journal of Traditional Chinese Medicine*. 2003;23(2):134-135.

Chen YQ. Yanreqing injection in the treatment of 24 patients with infectious mononucleosis. *TCM Research*. 2005;18(7):45-6.

de Ruyter P. Herbalism: a potent tool in management of chronic fatigue syndrome. *1995 NHAA (National Herbalists Association of Australia) International Conference*. 1995:77-80.

de Sylva R. Herbal therapeutics and treatment of chronic fatigue syndrome, Epstein-Barr virus and Candida albicans. *1992 NHAA (National Herbalists Association of Australia) International Conference*. 1992:14-18.

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629-634.

Egger M, Dickersin K, Smith George. Problems and limitations in conducting systematic reviews. In: *Systematic Reviews in Health Care: Meta-analysis in Context***,** M. Egger, G. Smith, and D. Altman Eds. London UK: BMJ Books, 2001 p43-64.

Egger M, Smith G. Meta-analysis bias in location and selection of studies. *BMJ.* 1998;316:61-66.

Fan WY, Tong YY, Pan YL, Shang WL, Shen JY, Li LJ. Traditional Chinese medical journals currently published in Mainland China. *The Journal of Alternative and Complementary Medicine*. 2008;14(5) :595-609.

Feng SJ, Ma QJ, Meng Y, Chen MM, Bi XY. Clinical study of feet massage in the intervention of chronic fatigue syndrome. *Shandong Journal of Traditional Chinese Medicine*. 2005;24(5):288-290.

Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, Komaroff A et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine.* 1994;121:953-959.

Fung I. Chinese journals: a guide for epidemiologists. *Emerging Themes in Epidemiology*. 2008;5:20.

Gou CY, Tian FW, Li N. Clinical study of moxibustion following channels in the treatment of chronic fatigue syndrome. *Journal of Sichuan of Traditional Chinese Medicine.* 2004;22(3):87-8.

Gui SQ. Comparative observation for the effect of reflect method in the treatment of chronic fatigue syndrome. *Foot and Care Journal*. 2003;6:9-10.

Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-560.

Hill S. The superwoman and the victim: a discussion of two cases of ME. *European Journal of Oriental Medicine*. 1994;2(1):46-49.

Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE et al. Chronic fatigue syndrome: A working case definition. *Annals of Internal Medicine.* 1988;108:387-389.

Ioannidis J, Haidich A, Pappa M, Pantazis N, Kokori S, Tektonidou M, et.al. Comparison of evidence of treatment effects in randomizd and non-randomized studies. *Journal of the American Medical Association.* 2001;286:821-830.

Jadad A. *Randomized Controlled Trials: A Users Guide.* London UK: BMJ Books, 1998 p 30-37.

Jiao YX, Li YT, Zhao Q. Liaoshen Daoqi method in the treatment of 36 patients with chronic fatigue syndrome. *Journal of Acupuncture Clinical Practice*. 2006;22(12):51-52.

Juni P, Egger M. Letter to the editor. *Journal of the American Medical Association.* 2002;288(19):2407-2408.

Kang FC, Luo XY. Observation for the effect of Yiqi Yangyin method in the treatment of 30 patients with CFS. *International Medicine and Health Guidance Newsreative Company*. 2006;12(22):43-44.

Khan K, Daya S, Collins J, Walter S. Empirical evidence of bias in infertility research: overestimation of treatment effect in crossover trials using pregnancy as the outcome measure. *Fertility and Sterility.* 1996;65(5):939-45.

Kunz R, Oxaman A. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ.* 1998;317:1185-90.

Li YM, Liu HP, Feng SL, Gong DF. Observation for the effect of electronic acupuncture with ear points in the treatment with 32 patients with chronic fatigue syndrome. *New Journal of Traditional Chinese Medicine*. 2005;37(1):61-2.

Li Y, Wu TX, Shang H, Yang K. Strategies for promoting the development of evidence based medicine in China. *Journal of Evidence-Based Medicine*. 2009;2(1):47-52.

Liang G. Clinical observation of variated Shengmai powder and Xuefuzhuyu decoction in the treatment of 63 patients with CFS. *Lishizen Medicine and Materia Medica Research*. 2006;17(5):801-2.

Lijue Z. Acupuncture and Chinese patent drugs for treatment of chronic fatigue syndrome. *Journal of Traditional Chinese Medicine*. 2005;25(2):99-101.

Liu XE. Pudilan Xiaoyan Oral Decoction as an adjunct drug in the treatment of infectious mononucleosis. *Modern Journal of Integrated TCM and WM*. 2007;16(18):2511-2512.

Liu YY. Acupuncture and cupping in the treatment of 40 patients with chronic fatigue syndrome. *Journal of Acupuncture and Moxibustion*. 2006;22(7):22-23.

Lloyd A, Hickie I, Boughton R, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. *Medical Journal of Australia.* 1990;153:522-528.

Lu YJ, Wang WH. Acupuncture and cupping in the treatment of 25 patients with chronic fatigue syndrome. *Shandong Journal of Traditional Chinese Medicine*. 2001;20(5):350-351.

Luo CG, Zhou ZB, Wen WQ, Yu YM. Flip and dial following bladder channels in the treatment of 30 patients with chronic fatigue syndrome. *Chinese Manipulation & Qi Gong Therapy*. 2006;22(3):4-6.

Manheimer E, Ezzo J, Hadhazy V, Berman B. Published reports of acupuncture trials showed important limitations. *Journal of Clinical Epidemiology*. 2006;59(2):107-13.

Meng H, Zhao WH. Clinical observation of traditional Chinese medicine with manipulation in the treatment of chronic fatigue syndrome. *Academic Periodical of Changchun College of Traditional Chinese Medicine*. 2006;22(1):20-21.

Mo MH. Qinkaining in the treatment of children with infectious mononucleosis. *China Medical Herald.* 2007;4(2):87-8.

Moher D, Fortin P. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet.* 1996;347(8998):363-366.

Moher D, Pham B, Klassen T, Schulz K, Berlin J, Jadad A, Liberati A. What contributions do languages other than English make on the results of meta-analyses? *Journal of Clinical Epidemiology.* 2000;53:964-972.

Moher D, Sampson M, Campbell K, Beckner W, Lepage L, Gaboury I, Berman B. Assessing the quality of reports of randomized trials in pediatric complementary and alternative medicine. *BMC Pediatrics.* 2002;2:1471-2431/2/2.

Ni KQ. Acupuncture and TCM in the treatment of 35 patients with chronic fatigue syndrome. *Journal of Fujian College of TCM*. 2002;12(4):22.

Ning TC, Li YP. Variated Sijunzi decoction in the treatment of 23 patients with chronic fatigue syndrome. *Research of Traditional Chinese Medicine*. 2002;18(4):16-17.

Pan CQ, Tang ZG, Tan GB. Electronic acupuncture with acupoint shot in the treatment of 35 patients with chronic fatigue syndrome. *Hunan Journal of TCM.* 2005;21(6):22-3.

Peng ZY. Shenmai injection in the treatment of patients with chronic fatigue syndrome. *Modern Integrated Traditional Chinese and Western Medicine Journal*. 2000;9(8):684-685.

Pham B, Klassen T, Lawson M, Moher D. Language of publication restrictions in systematic reviews gave different results depending on whether the intervention

was conventional or complementary. *Journal of Clinical Epidemiology.* 2005;58:769-76.

Pilkington K, Boshnakova A, Clarke M, Richardson J. "No language restrictions" in database searches: what does this really mean? *Journal of Alternative and Complementary Medicine*. 2005;11(1):205-7.

Pu YF, Zhang XL, Shen AH. Observation for the effect of Huangqi injection in the treatment of 43 patients with chronic fatigue syndrome. *Modern Journal of Integrated Traditional Chinese and Western Medicine*. 2002;11(3):224.

Schulz K, Chalmers I, Hayes R, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association.* 1995;273:408-12.

Sharpe M, Archard L, Banatvala J et al. Chronic fatigue syndrome: guidelines for research. *Journal of the Royal Society of Medicine.* 1991;84:118-121.

Shekelle P, Morton S, Suttorp M, Buscemi N, Friesen C. Challenges in systematic reviews of CAM topics. *Annals of Internal Medicine*. 2005;42(12):1042-1050.

Shi YL, Fu RH. Procussion puncture on "Naochong three line" in the treatment of 52 patients with chronic fatigue syndrome. *Zhejiang Journal of TCM*. 2004;10(2):448.

Shu YQ, Zhang GL. Treating 30 cases of chronic fatigue syndrome with modified Buzhong Yiqi decoction. *Journal of Anhui College of TCM*. 1997;16(5):11-12.

Sierpina V, Carter R. Alternative and integrative treatment of fibromyalgia and chronic fatigue syndrome. *Clinics in Family Practice*. 2002;4(4):853-872.

Statistics Canada. Health Report: use of alternative health care. *The Daily.* 2004;16(2) http://dsp-psd.pwgsc.gc.ca/Collection-R/Statcan/82-003-XIE/0020482-003-XIE.pdf

Sun LF, Hao L, Li L. Observations on the curative effect of Naoshenkang capsule in the treatment of 354 patients with chronic fatigue syndrome. *Hebei Journal of Traditional Chinese Medicine*. 2005;27(4):261-262.

Sun G. Integrated TCM and WM in the treatment of 23 patients with infectious mononucleosis. *Chinese Folk Therapy*. 2006;14(10):4.

Tang J, Zhan S, Ernst E. Review of RCTs of TCM. *BMJ.* 1999;319:160-161.

Tian HZ, Chen JL. Effect on immunologic function of Ai Jiu Qiangzhuang acupoint in the treatment of patients with CFS. *Shenzhen Journal of Integrated Traditional Chinese and Western Medicine.* 2006;16(4):226-227.

Vickers A, Goyal N, Harland R, Rees R. Do certain countries produce only positive results? A systematic review of controlled trials. *Controlled Clinical Trials.* 1998;19:159-166.

Wang AS. Qinrejiedu and Huoxuehuayu therapy for children with infectious mononucleosis. *Association of Chinese Medicine Practitioners.* 2006;34(2):16.

Wang N. Clinical analysis of Zhonghuichuanghuang liquid in the treatment of chronic fatigue syndrome. *Modern Journal of Integrated Chinese and Western Medicine*. 2004;13(1):53-54.

Wang N, Dan YF. Clinical observation of Xianqi decoction in the treatment of chronic fatigue syndrome. *Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine*. 2006;6(2):31-32,37.

Wang WY. Variable Caihutang in the treatment of 24 patients with infectious mononucleosis. *Chinese TCM Science and Technique*. 2000;7(6):412-413.

Wei LL. Clinical observation of Xiaocaihu decoction in the treatment of CFS. *Chinese Archives of Traditional Chinese Medicine*. 2005;23(7):1315-1317.

World Health Organization (WHO). *Traditional Medicine Strategy 2002–2005*. Geneva, Switzerland: World Health Organization Publishing, 2002.

WuT, Li Y, Bian Z, Liu G, Li J, Moher D. Randomized trials published in some Chinese journal: how many are randomized? *Trials.* 2009;10(46);doi:10 .1186/1745-6215-10-46.

Xia J, Wright J, Adams C. Five large Chinese biomedical bibliographic databases: accessibility and coverage. *Health Information and Libraries Journal*. 2008;25:55-61.

Xiong FL, Xiao YP. Acupoints shot by using Huangqi injection in the treatment of 32 patients with chronic fatigue syndrome. *Guangxi Journal of TCM*. 2000;23(6):30-31.

Yan S. Qinkaining in the treatment of 55 patients with infectious mononucleosis. *TCM Clinical*. 2006;21(6):43.

Yan XH. Treatment of 45 cases of infantile infectious mononucleosis with heat - clearing and detoxifying resolving phlegm by removing blood stasis drugs. *Hunan Guiding Journal of TCMP.* 2000;6(3):7-8.

Yang RX. Kuhanjiedu therapy in the treatment of children with infectious mononucleosis. *Journal of Sichuan TCM*. 2007;25(8):2-3.

Yang SH, Gao M, Yang XW, Chen DQ. Clinical observation of the treatment of chronic fatigue syndrome by using BuzhongYiqi decoction in combination with Xiaochaihu decoction. *Journal of Beijing University of TCM.* 2004;27(2):87-89.

Yang XH. Integrated TCM and WM in the treatment of 40 children with infectious mononucleosis. *Guizhou Medical Journal*. 2007;31(10):4-5.

Yao RM, Qiu MY. Clinical observation of chronic fatigue syndrome treated by Chinese medicine in Hong Kong. *Shanghai Journal of TCM*. 2005;39(6):12-13.

Yiu YM, Ng SM, Tsui YL, Chan YL. A clinical trial of acupuncture for treating chronic fatigue syndrome in Hong Kong. *Journal of Chinese Integrative Medicine*. 2007;5(6):630-633.

York University Centre for Health Studies. *Complementary and Alternative Practices and Therapies – A Canadian Overview.* Toronto, ON: York University Press, 1999.

Yuan SG, Zhao CW. Observations on the curative effect of traditional Chinese medicine in the treatment of chronic fatigue syndrome. *Chinese Journal of Information on Traditional Chinese Medicine*. 2006;13(8):57.

Zen J. TCM in the treatment of 35 children with infectious mononucleosis. *Journal of Practical TCM*. 2005;21(2):77.

Zhang R, Li J, Chen J, Zhang ZJ, Guo ZH. Clinical observation in the treatment of Shenqi Fuyuan decoction in the treatment of patient with chronic fatigue syndrome. *Chinese Journal of TCM Information*. 2004;11(2):148.

Zhang SX, Zhou W. Buzhong Yiqi decoction in the treatment of 40 patients with chronic fatigue syndrome. *Journal of Primary Medicine and Pharmacology*. 2004;11(5):608.

Zhang YM. TCM in the treatment of 40 children with infectious mononucleosis. Chinese *Journal of Integrated TCM and WM Emergency.* 2000;7(5):299.

Zhang ZH. Redujing in the treatment of 35 children with infectious mononucleosis. *Chinese Physician.* 2006;34(4):34-35.

Zhao DF, Duan HD, Zhao JW. Observation for the effect of Yiqi Yangyin method in the treatment of 30 patients with CFS. *Tianjin Journal of Traditional Chinese Medicine.* 2006;23(2):126-127.

2.7 Appendices

Appendix 2.1: Infectious Mononucleosis Search Terms (by database)

English-language databases – searches last updated June 17, 2008

MEDLINE & CENTRAL

randomized controlled trial, controlled clinical trial, randomized controlled trials/, random allocation/, double blind method/, single-blind method/, clinical trial, exp clinical trials/, (clin$ adj25 trial$), ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)), placebos/, placebo$, random$, research design/, comparative study/, exp evaluation studies/, follow up studies/, prospective studies/, (control$ or prospectiv$ or volunteer$); limit to human
AND
acupressure/, exp acupuncture therapy/, "channels and collaterals", qi, qi/, (chinese adj1 (diagnos$ or extract$ or formula$ or herb$)), (Chinese adj2 (medical or medicin$)), (cupping adj1 (treatment or therapy)), Drugs, Chinese Herbal/, Huang qi, Medicine, kampo/, Medicine, Chinese traditional/, medicine, oriental traditional/, Meridian doctrine, Moxibustion/, moxibustion, Oriental massage, qigong, tai ji/, tai chi, five element theory, Tongue diagnosis, (Traditional Chinese adj (medicine or medical)), Tuina, vital energy, Yang deficiency/, Yin deficiency/, yin-yang, shenmai, pulse, tcm
AND
Epstein Barr, infectious mononucleosis, mononucleosis, glandular fever

EMBASE

Randomized Controlled Trial/, exp Randomization/, Double Blind Procedure/, Single Blind Procedure/, Clinical Trial/, (clin$ adj25 trial$), ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)), exp Placebo/, (placebo$ or random$), exp Methodology/, exp Comparative Study/, exp Evaluation/, exp Follow Up/, exp Prospective Study/, (control$ or prospectiv$ or volunteer$); limit to human
AND
exp chinese medicine/, exp acupuncture/, ((chinese or chinese medic$ or tcm) adj25 (diagnos$ or exercise or diet or nutrition or food$ or breath$ or herb$ or massage$ or plant$ or channel$ or phytotherap$ or pulse or tongue or drug$ or needl$ or formula$ or botanic$)), (Chinese adj2 (medical or medicin$)), (cupping adj1 (treatment or therapy)), kampo/, (moxabustion or moxibustion), (oriental adj2 (medical or medicin$)), qi, qigong, (shiatsu or shiatzu), tai chi/, Tai ji, five element theory, Tongue diagnosis, pulse diagnosis, (Traditional Chinese adj (medicine or medical)), Tuina, vital energy, Yang, Yin, tcm\
AND
Epstein Barr, infectious mononucleosis, mononucleosis, glandular fever

AMED

random$, placebo$, ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or dummy or mask$)), crossover, assign$, allocat$, ((clin$ or control$ or compar$ or evaluat$ or prospectiv$) adj25 (trial$ or studi$ or study)), exp placebo/
AND
exp traditional medicine chinese/, exp acupuncture/, acupressure/, exp acupuncture therapy/, qi, qi/, (Chinese adj2 (medical or medicin$)), ((chinese or chinese medic$ or tcm) adj25 (diagnos$ or exercise$ or diet or nutrition$ or food or breath$ or herb$ or massage$ or plant$ of channel$ or phytotherap$ or pulse or tongue or drug$ or needl$ or formula$ or botanic$)), (cupping adj1 (treatment or therapy)), exp Drugs, Chinese Herbal/, Medicine, kampo/, (Chinese adj2 Medicin$), Moxibustion/, qigong, (shiatsu or shiatzu), tai chi, five element theory, Tongue diagnosis, (Traditional Chinese adj (medicine or medical)), Tuina, vital energy, yin-yang, Shenmai, tcm
AND
Epstein Barr, infectious mononucleosis, mononucleosis, glandular fever

CINAHL

random sample, random assignment, cross over or crossover or cross-over, clinical trials+, comparative studies+, "control (research)", control group, factorial design, quasi-experimental stud*, nonrandom* trial*, placebo*, meta analys*, clinical nursing research or clinical research, community trials or experimental stud* or one-shot case stud*, pretest-posttest design or solomon four-group design or static group comparison or study design, pt clinical trial or pt systematic review, random*, placebo* or control* or factorial or sham*, metanaly* or meta analy* or meta-analy*, clin* N10 trial* or intervention* N10 trial* or compar* N10 trial* or experiment* N10 trial* or preventive N10 trial* or therapeutic N10 trial*, singl* N10 blind* or doubl* N10 blind* or tripl* N10 blind*, singl* N10 mask* or doubl* N10 mask* or tripl* N10 mask*, systematic review*, convenience sample, research, allied health+ or research, medical+ or research, nursing+, research question, nursing practice, research-based, research methodology, evaluation research+, concurrent prospective studies or prospective studies, pt nursing interventions or pt nursing research
AND
medicine, oriental traditional+, medicine, chinese traditional+, tcm, chinese N2 medical or chinese N2 medicin*, acupuncture+, acupressure+, moxibustion+, qigong+ or qi gong+, qi, oriental N1 massage or chinese N1 massage or asian N1 massage, tui na+, tui na or tuina, "channels and collaterals", cupping N1 treatment or cupping N1 therapy, meridian doctrine, tai chi+, tai chi or tai ji, chinese N1 diagnos*, chinese N1 extract* or chinese N1 formula* or chinese N1 herb*, drugs, chinese herbal+, five element theory, tongue diagnosis, yin-yang,
AND
Epstein Barr, infectious mononucleosis, mononucleosis, glandular fever

PSYCHINFO

random$, ((singl$ or doubl$ or treble$ or tripl$) adj25 (blind$ or dummy or mask$)), placebo$, crossover, assign$, allocat$, ((clin$ or control$ or compar$ or evaluat$ or prospectiv$) adj25 (trial$ or studi$ or study)), exp placebo/, exp treatment effectiveness evaluation/, exp mental health program evaluation/, exp experimental design/, (human or inpatient or outpatient); limit to human
AND
qi, chinese diagnos$, chinese extract$, Chinese formula$, Chinese herb$, (Chinese adj2 (medical or medicin$)), (cupping adj1 (treatment or therapy)), exp Acupuncture/, moxibustion, acupuncture, acupressure, moxibustion, qigong, (shiatsu or shiatzu), ((oriental or asian or chinese) and massage), tai chi, tai ji, Tongue diagnosis, (Traditional Chinese adj (medicine or medical)), chinese medicine, traditional chinese medicine, tcm, vital energy, yin-yang
AND
Epstein Barr, infectious mononucleosis, mononucleosis, glandular fever

The Cochrane Depression, Anxiety and Neurosis Group Controlled Trials Registers: CCDAN

CCDANCTR-**Studies**
Diagnosis = Fatigue or Neurasthenia and Intervention = "Traditional Chinese Medicine" or acup* or chi or "ch'i" or qi or cupping or Kampo or Meridian or Moxibus* or Moxabus* or qigong or tai or taichi or Tuina or Yin or Yang or Shenmai or "Tongue Diagnosis" or "Five Element"

CCDANCTR-**References**
Keyword = Fatigue or Neurasthenia or Free-text = CFS and Title or Abstract or Keyword = Chinese or Title or Abstract or Keyword = Traditional

Proceedings First, Proquest Dissertations, PapersFirst

(Chinese or asian or oriental) or (acupuncture or acupressure or moxibustion or moxa) or (herb* or massage or tuina or qi or qigong or tai chi or tai ji) or (tcm or kampo or (Chinese medicine) or (oriental medicine) or (traditional medicine))
AND
infectious mono* or mono or glandular fever

Chalmers Research Group PedCAM Database was hand searched

Chinese-language Databases: run Jan 10, 2008

VIP Knowledge Network & CNKI

traditional Chinese medicine, herbs, herbal medicine, acupuncture, electronic acupuncture, acupressure, tuina, tai ji, qi gong, moxibustion, huo guan **AND** Epstein barr virus infection **OR** Infectious mononucleosis

Appendix 2.2: ICF/CFS Search Terms

(by database)

English-language databases – run Jan 2008

MEDLINE & CENTRAL

randomized controlled trial, controlled clinical trial, randomized controlled trials/, random allocation/, double blind method/, single-blind method/, clinical trial, exp clinical trials/, (clin$ adj25 trial$), ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)), placebos/, placebo$, random$, research design/, comparative study/, exp evaluation studies/, follow up studies/, prospective studies/, (control$ or prospectiv$ or volunteer$); limit to human

AND

acupressure/, exp acupuncture therapy/, "channels and collaterals", qi, qi/, (chinese adj1 (diagnos$ or extract$ or formula$ or herb$)), (Chinese adj2 (medical or medicin$)), (cupping adj1 (treatment or therapy)), Drugs, Chinese Herbal/, Huang qi, Medicine, kampo/, Medicine, Chinese traditional/, medicine, oriental traditional/, Meridian doctrine, Moxibustion/, moxibustion, Oriental massage, qigong, tai ji/, tai chi, five element theory, Tongue diagnosis, (Traditional Chinese adj (medicine or medical)), Tuina, vital energy, Yang deficiency/, Yin deficiency/, yin-yang, shenmai, pulse, tcm

AND

idiopathic chronic fatigue, unexplained chronic fatigue, exp Fatigue Syndrome, Chronic/, exp Fatigue/, (fatigue$ or apath$ or asthenia or exhaust$ or languor$ or lassitude or letharg$ or malaise or tired$), chronic fatigue, fatigue syndrome, chronic fatigue immune dysfunction syndrome, (chronic fatigue and immune dysfunction syndrome), exp neurasthenia/, neurasthenia, myalgic encephalomyelitis, post-viral fatigue syndrome, post-infective fatigue syndrome, chronic Epstein-Barr virus infection, chronic Epstein-Barr virus syndrome, chronic Epstein-Barr virus infection syndrome, chronic mononucleosis, Iceland disease, Royal Free disease, exp Neurocirculatory Asthenia/, effort syndrome, Soldier s Heart, Da Costa's syndrome, immun$ deficiency syndrome, CFIDS, CFS, ICF, EBV syndrome

EMBASE

Randomized Controlled Trial/, exp Randomization/, Double Blind Procedure/, Single Blind Procedure/, Clinical Trial/, (clin$ adj25 trial$), ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)), exp Placebo/, (placebo$ or random$), exp Methodology/, exp Comparative Study/, exp Evaluation/, exp Follow Up/, exp Prospective Study/, (control$ or prospectiv$ or volunteer$); limit to human

AND

exp chinese medicine/, exp acupuncture/, ((chinese or chinese medic$ or tcm) adj25 (diagnos$ or exercise or diet or nutrition or food$ or breath$ or herb$ or massage$ or plant$ or channel$ or phytotherap$ or pulse or tongue or drug$ or needl$ or formula$ or botanic$)), (Chinese adj2 (medical or medicin$)), (cupping adj1 (treatment or therapy)), kampo/, (moxabustion or moxibustion), (oriental adj2 (medical or medicin$)), qi, qigong, (shiatsu or shiatzu), tai chi/, Tai ji, five element theory, Tongue diagnosis, pulse diagnosis, (Traditional Chinese adj (medicine or medical)), Tuina, vital energy, Yang, Yin, tcm\

AND

idiopathic chronic fatigue, exp chronic fatigue syndrome/, exp Fatigue/, (fatigue$ or apath$ or asthenia or exhaust$ or languor$ or lassitude or letharg$ or malaise or tired$), chronic fatigue, fatigue syndrome, chronic fatigue immune dysfunction syndrome, (chronic fatigue and immune dysfunction syndrome), exp neurasthenia/, neurasthenia, myalgic encephalomyelitis, post-viral fatigue syndrome, chronic Epstein-Barr virus infection, chronic Epstein-Barr virus syndrome, chronic mononucleosis, Iceland disease, Royal Free disease, exp Neurocirculatory Asthenia/, effort syndrome, CFIDS, CFS, ICF, ME, EBV syndrome

AMED

random$, placebo$, ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or dummy or mask$)), crossover, assign$, allocat$, ((clin$ or control$ or compar$ or evaluat$ or prospectiv$) adj25 (trial$ or studi$ or study)), exp placebo/
AND
exp traditional medicine chinese/, exp acupuncture/, acupressure/, exp acupuncture therapy/, qi, qi/, (Chinese adj2 (medical or medicin$)), ((chinese or chinese medic$ or tcm) adj25 (diagnos$ or exercise$ or diet or nutrition$ or food or breath$ or herb$ or massage$ or plant$ of channel$ or phytotherap$ or pulse or tongue or drug$ or needl$ or formula$ or botanic$)), (cupping adj1 (treatment or therapy)), exp Drugs, Chinese Herbal/, Medicine, kampo/, (Chinese adj2 Medicin$), Moxibustion/, qigong, (shiatsu or shiatzu), tai chi, five element theory, Tongue diagnosis, (Traditional Chinese adj (medicine or medical)), Tuina, vital energy, yin-yang, Shenmai, tcm
AND
idiopathic chronic fatigue, unexplained chronic fatigue, exp Fatigue Syndrome, Chronic/, exp Fatigue/, (fatigue$ or apath$ or asthenia or exhaust$ or languor$ or lassitude or letharg$ or malaise or tired$), chronic fatigue, fatigue syndrome, chronic fatigue immune dysfunction syndrome, neurasthenia, myalgic encephalomyelitis, post-viral fatigue syndrome, chronic Epstein-Barr virus infection, chronic Epstein-Barr virus syndrome, chronic mononucleosis, Iceland disease, Royal Free disease, effort syndrome, Da Costa's syndrome, immun$ deficiency syndrome, CFIDS, CFS, ICF, ME

CINAHL

random sample, random assignment, cross over or crossover or cross-over, clinical trials+, comparative studies+, "control (research)", control group, factorial design, quasi-experimental stud*, nonrandom* trial*, placebo*, meta analys*, clinical nursing research or clinical research, community trials or experimental stud* or one-shot case stud*, pretest-posttest design or solomon four-group design or static group comparison or study design, pt clinical trial or pt systematic review, random*, placebo* or control* or factorial or sham*, metanaly* or meta analy* or meta-analy*, clin* N10 trial* or intervention* N10 trial* or compar* N10 trial* or experiment* N10 trial* or preventive N10 trial* or therapeutic N10 trial*, singl* N10 blind* or doubl* N10 blind* or tripl* N10 blind*, singl* N10 mask* or doubl* N10 mask* or tripl* N10 mask*, systematic review*, convenience sample, research, allied health+ or research, medical+ or research, nursing+, research question, nursing practice, research-based, research methodology, evaluation research+, concurrent prospective studies or prospective studies, pt nursing interventions or pt nursing research

AND

medicine, oriental traditional+, medicine, chinese traditional+, tcm, chinese N2 medical or chinese N2 medicin*, acupuncture+, acupressure+, moxibustion+, qigong+ or qi gong+, qi, oriental N1 massage or chinese N1 massage or asian N1 massage, tui na+, tui na or tuina, "channels and collaterals", cupping N1 treatment or cupping N1 therapy, meridian doctrine, tai chi+, tai chi or tai ji, chinese N1 diagnos*, chinese N1 extract* or chinese N1 formula* or chinese N1 herb*, drugs, chinese herbal+, five element theory, tongue diagnosis, yin-yang

AND

fatigue* or apath* or asthenia or exhaust* or languor* or lassitude or letharg*or malaise or tired*, fatigue+, fatigue syndrome, chronic+, chronic fatigue syndrome, chronic fatigue, fatigue syndrome, idiopathic chronic fatigue, unexplained chronic fatigue, chronic fatigue immune dysfunction syndrome, "chronic fatigue and immune dysfunction syndrome", neurasthenia, myalgic encephalomyelitis, post-viral fatigue syndrome, chronic Epstein-Barr virus infection, chronic Epstein-Barr virus syndrome, chronic mononucleosis, iceland disease, royal free disease, effort syndrome, immun* deficiency syndrome, CFIDS, CFS, ICF

PSYCHINFO

random$, ((singl$ or doubl$ or treble$ or tripl$) adj25 (blind$ or dummy or mask$)), placebo$, crossover, assign$, allocat$, ((clin$ or control$ or compar$ or evaluat$ or prospectiv$) adj25 (trial$ or studi$ or study)), exp placebo/, exp treatment effectiveness evaluation/, exp mental health program evaluation/, exp experimental design/, (human or inpatient or outpatient); limit to human
AND
qi, chinese diagnos$, chinese extract$, Chinese formula$, Chinese herb$, (Chinese adj2 (medical or medicin$)), (cupping adj1 (treatment or therapy)), exp Acupuncture/, moxibustion, acupuncture, acupressure, moxibustion, qigong, (shiatsu or shiatzu), ((oriental or asian or chinese) and massage), tai chi, tai ji, Tongue diagnosis, (Traditional Chinese adj (medicine or medical)), chinese medicine, traditional chinese medicine, tcm, vital energy, yin-yang
AND
exp Fatigue/, chronic fatigue, fatigue syndrome, chronic fatigue immune dysfunction syndrome, exp Fibromyalgia/, exp neurasthenia/, neurasthenia, myalgic encephalomyelitis, post-viral fatigue syndrome, chronic Epstein-Barr virus infection, chronic mononucleosis, Iceland disease, effort syndrome, CFIDS, CFS, ICF, ME, (fatigue$ or apath$ or asthenia or exhaust$ or languor$ or lassitude or letharg$ or malaise or tired$), exp Chronic Fatigue Syndrome/, chronic fatigue syndrome, idiopathic chronic fatigue, unexplained chronic fatigue, chronic fatigue

The Cochrane Depression, Anxiety and Neurosis Group Controlled Trials Registers: CCDAN

CCDANCTR-**Studies**
Diagnosis = Fatigue or Neurasthenia and Intervention = "Traditional Chinese Medicine" or acup* or chi or "ch'i" or qi or cupping or Kampo or Meridian or Moxibus* or Moxabus* or qigong or tai or taichi or Tuina or Yin or Yang or Shenmai or "Tongue Diagnosis" or "Five Element"

CCDANCTR-**References**
Keyword = Fatigue or Neurasthenia or Free-text = CFS and Title or Abstract or Keyword = Chinese or Title or Abstract or Keyword = Traditional

Proceedings First, Proquest Dissertations & PapersFirst

acupuncture or acupressure or moxibustion or moxa or herb* or massage or tuina or qi or qigong or tai chi or tai ji or tcm or kampo or (Chinese medicine) or (oriental medicine) or (traditional medicine) **AND** fatigue* or apath* or asthenia or exhaust* or languor* or lasstitude or letharg* or malaise or tired*

Chalmers Research Group PedCAM Database was hand searched.

Chinese-language databases: run June 2008

VIP Information & CNKI

Fatigue, chronic fatigue, chronic fatigue syndrome **AND** traditional Chinese medicine, herbs, herbal medicine, acupuncture, electronic acupuncture, acupressure, tuina, tai ji, qi gong, moxibustion, huo guan **AND** random, random$ control$, control$

Chapter 3: The Safety of Pediatric Acupuncture: A Systematic Review

3.1 Introduction

Acupuncture is a therapy that is believed to have developed in China over thousands of years and refers to the stimulation of precisely defined, specific points on meridians that run along the surface and interior of the body. Acu-points may be stimulated by a variety of techniques that include pressure, laser, application of heat, or insertion of thin needles (Flaws 1993). Stimulation of acu-points is believed to rebalance Qi and removed blockages to the proper flow of Qi through the meridians. Each acu-point has defined therapeutic actions; some points treat local symptoms while others treat broad imbalances. Although other forms of acupuncture are in practice, including Japanese acupuncture (where needles are generally inserted to very shallow depths), and Western medical acupuncture (where diagnosis and treatment follow Western medical models), traditional Chinese acupuncture is the most common form.

Needle acupuncture treatment may be varied according to many parameters, including point selection, number of points used, needle insertion depth, presence and method of needle manipulation, length of treatment time, and whether de chi is achieved or not (Kaptchuk 2002).

Acupuncture is commonly used in many parts of the world. For example, in Canada, 12% of people have used acupuncture at some point in their lives and 2% used acupuncture in 2003 (Statistics Canada 2004, York University 1999). A recent US study estimated adult use in 2007 at over three million people, up from approximately two million people in 2002. Specific patient populations have been shown to use acupuncture at much higher rates than the general public. Among US children, it is estimated that 150 000 used acupuncture in 2007 (Barnes 2008). Use among specific patient populations is frequently much higher.

While the efficacy of acupuncture in adults has been the subject of many reviews and meta-analyses (Afari 2003, Berman 2000, Birch 2004, Dincer 2003, Kaptchuk 2002, Leggett Tait 2002, Lewith 1983, Mayer 2000, Sanchez Araujo

1998, WHO 2002), evaluations of the efficacy of acupuncture in children are much less common (Gold 2009, Jindal 2008). In any therapeutic evaluation the risk/benefit ratio must be considered. In the absence of convincing evidence about efficacy of pediatric acupuncture, assessments of risk are paramount.

It is commonly believed that children will be intolerant of needle insertion, however, recent studies of pediatric pain clinic patients receiving needle acupuncture contradict this assumption (Kemper 2000, Tsao 2005, Zeltzer 2002). A number of hospitals in North America now routinely offer acupuncture to treat pain in pediatric oncology patients, including Seattle Children's Hospital, Boston Children's Hospital, and the Columbia University Medical Center in New York.

Acupuncture safety reviews have so far focused on adult populations. For example, a 2005 study of over 9400 adult patients collected data on short-term reactions to acupuncture (Macpherson 2005). Of the 15 745 reactions reported, 68% were positive 18% were negative and 14% were of tiredness or drowsiness. The rate of occurrence of these two categories of AEs was reported as 53.9/100 sessions, with tiredness/drowsiness and pain at insertion accounting for 24% and 12% respectively. Only 13 (0.14%) patients reported being unwilling to have acupuncture again because of their experiences. A meta-analysis reviewing the safety of acupuncture concluded that the risk of serious adverse events (AEs) associated with acupuncture were five per one million treatments (White 2004). It was not specified if this estimate included both adults and children but of the 12 studies in the meta-analysis, two included only adults and four included a small proportion of children, while for the remaining six studies, age-related information was not available from either the publications or from the authors. In all cases, details about the patients in whom the AEs occurred, including age, were not reported. Authors of acupuncture reviews generally agree that acupuncture is safe if carried out by properly trained practitioners, and no distinction has been made between adults and children in this conclusion (Berman 2000, BMA 2000, Kaptchuk 2002, Leggett Tait 2002, Melchart 2004, NIH 1997, WHO 2002, Yamashita 1998, Yamashita 1999, Yamashita 2008).

In a recent review of the literature, Jindal et al. presented a summary of pediatric acupuncture safety (Jindal 2008). Despite the fact that randomized controlled trials (RCTs) are known to underestimate rare harms (Egger 2001, Ioannidis 2004), this review was limited to RCT evidence of four different acu-point stimulation techniques, needle (with or without electrical stimulation) (5), laser (3), or acu-point injection (1). The authors identified a total of 29, predominantly mild, AEs occurring in either acupuncture treatment arms or acupuncture control arms and presented a combined AE incidence of 1.6/100 treatments sessions.

To our knowledge, a systematic review of pediatric acupuncture safety has not yet been published. The purpose of this review was to systematically collect and synthesize all published reports of pediatric AEs associated with needle acupuncture.

3.2 Methods

Data Sources

Comprehensive search strategies were developed in conjunction with a clinical librarian and run in 18 databases: MEDLINE (1950-2007), Cochrane Database of Systematic Reviews (1991-2007), HealthStar (1966-2007), EMBASE (1988-2007), Cochrane Central Registry of Controlled Trials (CENTRAL) (1991-2007), AMED (1985-2007), Acubriefs, Complementary and Alternative Medicine and Pain Database (CAMPAIN), Alternative Health Watch (1990-2007), CINAHL (1937-2007), Index to Chiropractic Literature (ICL) (1985-2007), MANTIS (1990-2007), PsycInfo (1806-2007), PUBMED (1950-2007), Scopus (1900-2007), Sport Discus (1975-2007), Web of Science (1990-2007), and the Online Computer Library Center Inc (OCLC) Dissertation Abstracts (1861-2007), from inception to June 2007, irrespective of language. Search terms are detailed in appendix 3.1. Reference lists of review articles and included studies were searched for additional studies.

Study Selection

Titles and abstracts of identified studies were independently screened by two reviewers. Full texts for potentially relevant studies were obtained and reviewed for inclusion based on predetermined criteria. Disagreement was resolved by discussion.

Studies were included if they: i) contained original patient data published in a peer-reviewed journal, ii) included children from birth to 17 years inclusive, iii) involved needle acupuncture, and iv) included a report of an adverse event in a child. Inclusion was not limited by any other variables.

Data Extraction

Data was extracted by one reviewer, using standardized forms, and verified by a second reviewer. Disagreement was resolved by discussion. The following information was extracted: author; year, country and language of publication; study design; number, age, and gender of participants; reasons for seeking acupuncture; co-morbid conditions and concomitant treatments; details of acupuncture and control treatments; practitioner qualifications; and details of AEs. If necessary, principal authors were contacted for further details.

Data Synthesis

AE severity was independently assessed by two reviewers and was based on the Common Terminology Criteria for Adverse Events (CTCAE) scale (NCI 2009). Categories were: mild (minor; no specific medical intervention), moderate (minimal, local, or non-invasive intervention), or serious (requires hospitalization or invasive procedures, results in persistent or significant disability/incapacity, is life-threatening, or results in death) (Appendix 3.2). Disagreement between reviewers was resolved by discussion and if necessary a third party was consulted.

The degree of association between the intervention and the AE was independently assessed by two reviewers, using the Causality Algorithm used by Health Canada and the WHO Collaborating Centre for International Drug Monitoring; terminology was modified for use in a physical intervention rather

than just for a drug (Health Canada 2009). Categories for assessment were: Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified, and Unassessible/Unclassifiable (Appendix 3.3). Disagreement between reviewers was resolved by discussion and if necessary a third party was consulted.

Results were presented as descriptive summaries. AEs in treatment and control groups (for two-arm studies) were tallied separately, in order to examine differences in incidence between these two groups. Because some acupuncture control groups used a different form of needle acupuncture as control, all AEs occurring in needle acupuncture groups, treatment or control, were also tallied. Differences in AE occurrence between groups were examined using Chi-square tests.

3.3 Results

Searches resulted in a total of 7262 references, of which 3425 were duplicates. After screening titles and abstracts of the remaining 3837 references the full texts of 209 articles were obtained. Of these, 15 articles representing 14 studies met all inclusion criteria (one study was published as two different articles). Five additional included studies were found through review of reference lists. Of the total of 20 included publications, 17 were published in English, while one each was published in Chinese, French, and Japanese.

Articles were excluded for the following reasons: full publication not available (4), no primary patient data (14), not human subjects (3), no children included (76), not involving needle acupuncture (37), and not reporting adverse events (60).

Of the 19 included studies, five were RCTs, five were cohort studies, and nine were case reports or case series. Fifteen studies included only pediatric patients, while four included adults as well. Of these, pediatric data were either presented separately (1) or further information on patient ages and AEs was obtained from study authors (3). The flow of articles through the review is shown in figure 3.1.

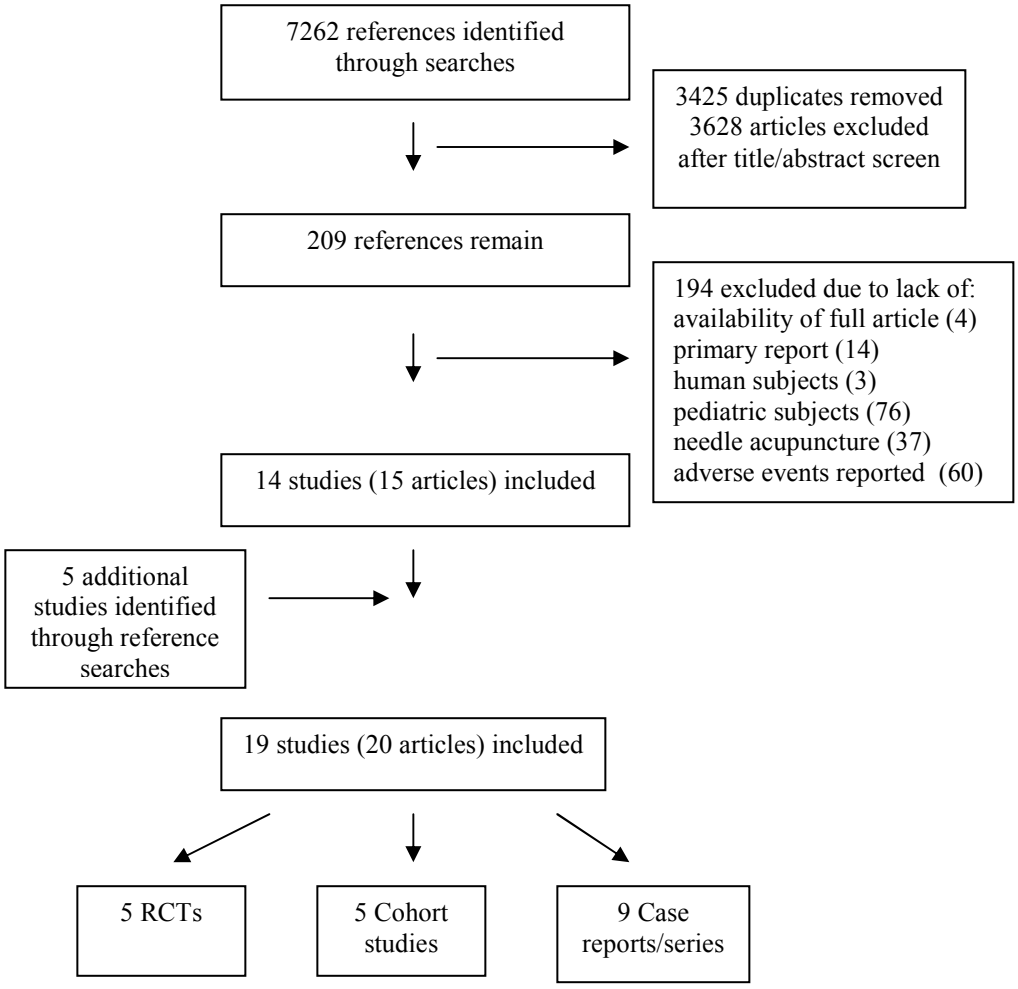

Figure 3.1: Flow of Studies Through Review

A total of 140 AEs were identified, 35 from the RCTs, 91 from the cohort studies, and 14 from the case reports/series. Of these, 133 were rated as mild and seven as serious. One serious AE was rated as unlikely to have been caused by the acupuncture. For the remaining AEs, 133 mild and six serious, causality was assessed as probable/likely or possible (Tables 3.1 and 3.2).

Serious Adverse Events

Seven pediatric AEs were rated as serious, one case each of cardiac rupture, pneumothorax, nerve impairment, three cases of infection, and one overnight hospitalization (Table 3.1).

In the case of cardiac rupture, a 9-year-old boy in China, suffering from malnutrition, was treated with acupuncture to the chest and abdomen, through his clothes. He was being treated for pre-existing conditions including pulmonary tuberculosis and heart disease, for which other care had failed. During the sixth treatment the boy experienced severe pain and died shortly after. The autopsy showed that the patient had a severely enlarged heart. Needle holes were found in the diaphragm, pericardium, and right ventricular wall, leading the examiner to conclude that death occurred due to puncture of the heart and subsequent rupture (Ye 1956).

In the case of the pneumothorax, a 15-year-old girl in France, being treated for acute asthma, experienced a pneumothorax during acupuncture treatment and was immediately hospitalized. The patient recovered and three months later signs of lung scarring were observed at the needling location (Carrette 1984).

In the case of limb numbness, a 16-year-old boy in Japan, experiencing fatigue, tachycardia, and constipation, was treated in such a way that over 70 needles were later found embedded in his body, one stuck in the spinal cord between the first and second cervical vertebrae. Symptoms of nerve impairment began soon after his treatment, progressing over two years to numbness in both legs and one arm. Surgery to remove the cervical needle resulted in good recovery from muscle weakness but sensation remained impaired (Sasaki 1984).

In the first case of infection, a 17-year-old male in France, being treated for tendonitis, was diagnosed with HIV infection. The first symptom (fever) developed during the week after his acupuncture treatments ended. Tests were suggestive of an early stage of infection and as all other risk factors for HIV had been excluded the infection was linked by the authors of the report to the preceding acupuncture treatment (Vittecoq 1989).

In the second case, a 14-year-old girl in Taiwan, being treated for mild glutteal pain, developed septic sacroiliitis within one day of acupuncture treatment, severe glutteal pain, and was unable to walk. After hospitalization and treatment with intravenous antibiotics and analgesics, her condition resolved within 10 days (Lau 1998).

In the third case, a 13-year-old boy in Japan, being treated for lumbar pain, developed fever and pain one day after acupuncture treatment and was diagnosed with septic arthritis of the lumbar facet joint. After hospitalization and treatment with antibiotics, his condition resolved within one week (Ishibe 2001).

The case of overnight hospitalization occurred during a randomized controlled trial of acupuncture for emesis related to dental anaesthesia, in Israel. The child (age and gender not reported) was admitted for excessive vomiting following dental treatment under general anaesthesia. The AE was rated as unlikely to be associated with acupuncture since three other patients were hospitalized for the same reason, one receiving ondansetron control and two receiving intravenous saline control (Somri 2001).

Mild Adverse Events

The 133 mild AEs included crying, pain, bruising, transient hemorrhage at the puncture site, numbness, aggravation of condition, and vasovagal reactions such as dizziness or nausea/vomiting (Table 3.2). Forty-two mild AEs occurred under treatment by acupuncturists, 64 by physicians certified in acupuncture, 19 by physicians whose acupuncture credentials were not reported, and eight by unspecified practitioners.

Thirty-four mild AEs occurred within RCTs, one in comparison to no treatment and the rest in comparison to sham acupuncture, which consisted of pressure or minimal penetration at active points. Fourteen of the mild AEs occurred in these acupuncture sham control groups.

Table 3.1: Serious Adverse Events

Adverse Event	Date; Location; Author	Number of Events	Age; Gender	Reason for Treatment	Practitioner	Association to treatment	Outcome
Randomized Controlled Trials							
Needle acupuncture versus ondansetron (IV) versus placebo (IV saline) for antiemesis from general anaesthesia during dental treatment in children aged 4-12 yrs; 49M, 41F, N=90 (30 per group); total N of treatment sessions = 11							
Overnight hospitalization for emesis	2001; Israel; Somri	1 acupuncture, 1 drug, 2 placebo	NR	Emesis from anaesthesia	Medical doctor licensed in TCM	Unlikely	Resolved
Case Reports							
Cardiac rupture	1956; China; Ye	1	9 yr, M	Tuberculosis, heart disease	Acupuncturist	Certain	Death
Pneumothorax	1984; France; Carette	1	15 yr, F	Asthma	Acupuncturist	Possible	Resolved
Nerve impairment	1984; Japan; Sasaki	1	16 yr at treatment, 18 yr at diagnosis of AE, M	Tiredness, rapid heartbeat, constipation	NR	Certain	Improvement after surgery
HIV infection	1989; France; Vittecoq	1	17 yr, M	Tendonitis	NR	Possible	Ongoing
Septic sacroiliitis	1998; Taiwan; Lau	1	14 yr, F	Mild pain in right buttock	NR	Possible	Resolved after antibiotics and hospitalization
Septic arthritis of lumbar facet joint	2001; Japan; Ishibe	1	13 yr, M	Pain in lumbar spine	Acupuncturist	Possible	Resolved after antibiotics and hospitalization

N = number; NR = not reported; M = male; F = female

Table 3.2: Mild Adverse Events

Adverse Event	Date; Location; Author	Number of events/ total N	Age; Gender	Time to Event	Practitioner	Association to Treatment
Randomized Controlled Trials						
Acubands followed by needle acupuncture at P6; sham acubands (no beads) followed by acupuncture at sham point for antiemesis from general anaesthesia during tonsillectomy, N=100 (47 treatment, 53 control), total N of treatment sessions = 47, 53; Age range 2-12 yr, mean 6.1 (2.4); 50M, 50F					Anaesthesiologist trained by a licensed acupuncturist	
Redness at site	1999; USA; Schenkman	9tx, 8ctr		NR		Certain
Irritation at site		1		NR		Certain
Crossover of TCM style acupuncture versus sham (minimal acupuncture at same points) for persistent allergic rhinitis, N=63 completed (32 treatment, 31 control); total N of treatment sessions = 512, 496; treatment gp age: 11.7 yr (3.2); Control gp age: 11 yr (3.8); 47M, 25F					Acupuncturist	
Numbness	2004; Hong Kong; Ng	3 tx, 2 ctr		NR		Certain
Headache		1 tx, 2 ctr		NR		Possible
Light-headedness		1 tx		NR		Possible
TCM acupuncture versus sham acupuncture (pressed needle on point but not inserted) of tongue points for cerebral palsy, N=33 (22 treatment, 11 control); total N of treatment sessions = 40; Treatment age: mean 8.62 yr (3.5); range 3.52-16.80 yr; control age: 10.68 yr (3.13); age range 4.47-14.09 yr; 16M, 17F					Acupuncturist	
Initial crying with fear and possible minor pain	2004; Hong Kong; Sun	4 tx, 2 ctr		At start of treatment		Possible
Crossover of needle or laser acupuncture versus no acupuncture for emetogenic chemotherapy, N=11, N of treatments = 22; Range 10 -16 yr; 4M, 7F					Acupuncturist	
Needle pain	2006; Germany; Reindl	1 tx		During treatment		Certain

Table 3.2: Mild Adverse Events (Continued)

Adverse Event	Date; Location; Author	Number of events/ total N	Age; Gender	Time to Event	Practitioner	Association to Treatment
Cohort Studies						
Fainting	1990; Taiwan; Chen	2/NR**	11-19 yr; NR	During treatment	NR	Probable
Hemorrhage (local)*	2000, 2001; Japan; Yamashita	≤6/8	10-19 yr; NR	Upon removal	Acupuncturist	Certain
Pain on insertion*		≤6/8		During treatment		Certain
Petechia or ecchymosis*		≤6/8		NR		Probable
Initial crying with fear and possible minor pain	2001; Hong Kong; Wong	3/10 patients or 300 treatments	7.3 yr (4.8); 5M, 5F	NR	Acupuncturist	Possible
Hematoma	2004; Germany; Endres	44/1109 patients or approx 11090 treatments@	2-17 yr; NR	NR	Medical doctor trained as an acupuncturist	Probable
Vasovagal reaction***		13/1109		NR		Possible
Drowsiness/sleep disturbance		1/1109		NR		Possible
Aggravation of condition		5/1109		NR		Possible
Sensation during treatment****		1/1109		During treatment		Probable
Initial crying with fear and possible minor pain	2006; Hong Kong; Wong	4/12 patients or 240 treatment	7.9 yr; 5M, 7F	NR	Acupuncturist	Possible

Table 3.2: Mild Adverse Events (Continued)

Adverse Event	Date; Location; Author	Number of events/ total N	Age; Gender	Time to Event	Practitioner	Association to Treatment
Case Reports/Series						
Petechiae – multiple	1972; USA; Buchta	1	2 yr, F	Treatment occurred 2 days prior to observation of petechiae; at least 2 days	Acupuncturist	Possible
Hemorrhages (local)	1993; China; Liu	~6/~20^	Under 18; NR	NR	NR	Certain
Prolonged migraine	1999; UK; Campbell	1	16 yr, M	NR	Medical doctor trained as an acupuncturist	Possible

N = total sample size; NR = not reported; M = male; F = female; tx = treatment; ctr = control; gp = group
*when contacted the author stated there were 8 pediatric patients in this study; up to 6 of whom had one or more of these 3 AEs (personal communication)
**This cohort study identified patients who fainted during treatment; of the 52 patients identified, 2 were children. The total number of patients treated was not reported; further information was not available from the author
*** including collapse, dizziness, nausea/vomiting
****Tingling/prickling/burning dysaesthesias, paraesthesia, hyperaesthesia not related to de qi sensation
@approx 10 sessions/patient
^when contacted the author stated that there were approximately 20 pediatric patients, of which approximately 6 had the AE

Adverse Event Incidence

A summary of AEs, based on study design, is presented in table 3.3. Incidences are presented based on the number of patients and the number of treatment sessions. Only those AEs rated as possibly, probably/likely, or certainly caused by acupuncture, from prospective studies, were included in the calculations.

Two of the four RCTs collected AEs in both the acupuncture treatment arms and the acupuncture control arms, while two more collected AEs in acupuncture treatment arms. The AEs in the four treatments arms totalled 20/112 patients (17.9%; 95% CI (10.8–25.0)) compared to 12/84 patients (14.3%; 95% CI (6.8–21.8)) in the two needle acupuncture control arms (p=0.56) (Ng 2004, Reindl 2006, Schenkman 1999, Sun 2004). Totalling the AEs for all needle acupuncture results in 32/196 patients (16.3%; 95% CI (11.2–21.5)). Presenting the same data based on the number of sessions, the rates become 20/1450 (1.4%; 95% CI (0.78–2.0)), 12/549 (2.2%; 95% CI (0.96–3.4)), and 32/1999 (1.6%; 95% CI (1.1–2.2)), respectively.

The third RCT compared needle acupuncture to acupressure and reported AEs in 4/22 patients (18.2%) or 4/880 sessions (0.05%) and 2/11 patients (18.2%) or 2/440 sessions (0.05%), respectively (Sun 2004). The fourth RCT, comparing acupuncture to no treatment, reported 1/11 (9.1%) and 0/11 patients, respectively (Reindl 2006).

Three cohort studies contributed usable AE data in relation to acupuncture treatment, totalling 71/1131 patients (6.3%; 95% CI (4.9–7.7)) and 71/11630 sessions (0.61%; 95% CI (0.47–0.75)), although one author estimated the number of sessions per patient so this rate must be interpreted with caution (Endres 2004). The three other cohort studies did not provide either reliable numerator or denominator values and were not included in the AE totals (Chen 1990, Liu 1993, Yamashita 2000).

Combining the AE data from both arms of all four RCTs and the three cohort studies resulted in a total of 105/1349 patients (7.8%; 95% CI (6.4–9.2)) or 105/14080 sessions (0.7%), while restricting data to only treatment and control

arms that provided needle acupuncture resulted in a total of 103/1327 patients (7.8%; 95% CI (6.4–9.2)) and 103/13629 sessions (0.76%; 95% CI (0.61–0.90)).

Table 3.3: Adverse Events Grouped by Study Design

Author; date	Treatment Arm AEs N/patient (%) N/session (%)	Control Arm AEs N/patient (%) N/session (%)	Total N/patient (%) N/session (%)
Randomized Controlled Trials			
Needle acupuncture in both arms			
Schenkman; 1999	10/47 (21.2%)	8/53 (15.1%)	18/100 (18%)
Ng; 2004	5/32 (15.6%) 5/512 (1.0%)	4/31 (12.9%) 4/496 (0.8%)	9/63 (14.3%) 9/1008 (0.9%)
Total **N/D; Rate/100** **95% CI**	**15/79; 18.9%;** **95% CI (10.3–27.6)** **15/559; 2.7%** **95% CI (1.3–4.0)**	**12/84; 14.3%** **95% CI (6.8–21.8)** **12/549 (2.2%)** **2.2 95% CI (0.96–3.4)**	**27/163; 16.6%** **95% CI (10.9–22.3)** **27/1108 (2.4%)** **2.4 95% CI (1.5–3.3)**
Needle acupuncture compared to acupressure			
Sun; 2004	4/22 (18.2%) 4/880 (0.5%)	2/11 (18.2%) 2/440 (0.5%)	6/33 (18.2%) 6/1320 (0.5%)
Needle acupuncture compared to no treatment			
Reindl; 2006	1/11 (9.1%)	0/11 (0%)	1/22 (4.5%)
RCT Total **N/D; Rate/100** **95% CI**	**20/112; 17.9%** **95% CI (10.8–25.0)** **20/1450; 1.4%** **95% CI (0.78–2.0)**	**14/106; 13.2%** **95% CI (6.8–19.7)** **14/1000; 1.4%** **95% CI (0.67–2.1)**	**34/218; 15.6%** **95% CI (10.8–20.4)** **34/2450; 1.4%** **95% CI (0.92–1.9)**
Single Arm Cohort Studies			
Wong; 2001	3/10 (33.3%) 3/300 (1.0%)	NA	3/10 (33.3%) 3/300 (1.0%)
Endres; 2004	64/1109 (5.8%) 64/11090* (0.6%)	NA	64/1109 (5.8%) 64/11090* (0.6%)
Wong; 2006	4/12 (33.3%) 4/240 (1.7%)	NA	4/12 (33.3%) 4/240 (1.7%)
Cohort Total **N/D; Rate/100** **95% CI**	**71/1131; 6.3%** **95% CI (4.9–7.7)** **71/11630; 0.61%** **95% CI (0.47–0.75)**	**NA**	**71/1131; 6.3%** **95% CI (4.9–7.7)** **71/11630; 0.61%** **95% CI (0.47–0.75)**
Overall Total **N/D; Rate/100** **95% CI**	**91/1243; 7.3%** **95% CI (5.9–8.8)** **91/13080; 0.70%** **95% CI (0.55–0.84)**	**14/106; 13.2%** **95% CI (6.8–19.7)** **14/1000; 1.4%** **95% CI (0.67–2.1)**	**105/1349; 7.8%** **95% CI (6.4–9.2)** **105/14080; 0.75%** **95% CI (0.60–0.89)**

AE = adverse events; RCT = randomized controlled clinical trial; NA = not applicable; N = numerator; D = denominator; CI = confidence interval;
*estimated number of sessions per patients

Excluded Studies

Six of the excluded studies were thought to be worthy of further mention in order to promote transparency in our decision-making. We excluded one report of the insertion of multiple metal objects by a practitioner described as an African 'specialist witchdoctor', which were detected when the patient was hospitalized for acute rheumatic fever (Oosthuysen 1979). As we were uncertain if this treatment qualified as acupuncture, we chose to exclude it. We also identified six studies that included both children and adults, however, despite multiple requests for additional information from the study authors, it remained unclear if any of the reported AE occurred in children, so these studies were not included. One of these studies included one child out of 41 patients (Fuller 1974), one study reported the mean age as 48 years with a range of 3-89 years (Cioppa 1976), one study reported that most patients were in their 40s with 5% under the age of 20 years (Yamashita 1999), one study included 794 children out of 14 340 (Umlauf 1988), and two studies included patients 17 years and older (Loh 1984, Yudkin 1996). These six studies reported more than 364 AEs (four serious, two moderate, and more than 358 mild). Because one study reported the AEs descriptively rather than numerically we are uncertain of the exact numbers (Cioppa 1976). Because the age of the patients experiencing the AEs was not reported these studies were not included. The four serious adverse events were two cases of pneumothorax and two cases of broken needles requiring surgical removal; the two moderate events were one case each of a small pneumothorax, which quickly resolved, and an injury to the elbow radial nerve. In this report the author summarized his practice experience and near the end mentioned these two adverse events without providing further details. The 364 mild AEs included pain, bruising, hemorrhage, fainting, worsened condition, hematoma, and nausea or vomiting.

3.4 Discussion

To our knowledge this is the first systematic review to specifically examine the safety of needle acupuncture in children. The majority of identified harms were mild and were from prospectively planned studies; few serious harms were identified.

A number of methods exist to classify or categorize harm, however, a standardized, broadly accepted method for categorizing the harms that may be associated with acupuncture is not yet in place despite earlier identification of such a need (MacPherson 1999). In order to be able to compare harms with other medical interventions we chose to use a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, which categorizes harm into mild, moderate, severe, life threatening, and death. We combined the last three categories and termed it 'serious'.

A recent publication on acupuncture safety discusses the occurrence of harms in acupuncture, classifying them as adverse effects or complications (Leung 2009). Adverse effects, in this context, are defined as unpredictable reactions to acupuncture, such as bleeding at puncture sites and vasovagal reactions, while complications refer to preventable events that may be related to practitioner negligence, including damage to tissues and organs under puncture sites. The authors reviewed the occurrence of AEs in eleven studies (comprising 2000 acupuncture sessions) conducted at their site over three years. The only adverse events were eight instances of transient bleeding at puncture sites, which led the authors to conclude that properly conducted acupuncture should not result in any complications.

In their 2004 safety review, White et al. collected AEs for the categories 'significant' (events that are unusual, novel, dangerous, or significantly inconvenient such as broken needles, seizures, or infection), or 'serious', which was defined more by the event consequences, which may include death, prolonged or new hospital admission, persistent or significant disability or incapacity, or threat to life (White 2004). The authors also discussed potential use of the terms 'unavoidable' (inherent to the procedure), 'avoidable' (those due to

technical error), 'indirect' (due to lack of medical knowledge), 'traumatic', 'infectious', and 'miscellaneous'. In their 2001 safety study, MacPherson et al. categorized AEs as 'mild transient' including bleeding, pain, and bruising at needle site, feeling drowsy, dizzy, nauseous, or faint, and aggravation of existing symptoms; 'significant minor' including severe nausea or vomiting, actual fainting, prolonged and unacceptable pain or bruising, avoidable errors, and unexpected, severe and prolonged aggravation of existing symptoms (Macpherson 2001). Classifications used by other authors include 'positive side effect', 'negative side effect', and 'complication' (Obsberg 2001), 'potentially serious' versus 'non-serious' (Melchart 2004), 'dangerous' versus 'harmless' (Ernst 2003), 'adverse reaction' versus 'negligence' (Yamashita 1999), or 'systemic reaction' versus 'local reaction' (Yamashita 2000).

In accordance with several of these suggested systems, five of the serious AEs we identified may have involved technical error rather than inherent risk from the procedure. The cases of infection may have occurred as a result of inadequate sterilization, either of site or needles, and the cases of cardiac rupture and pneumothorax as a result of improper technique or poor knowledge of anatomy. The case of cardiac rupture is particularly disturbing due to the numerous errors that were made, by modern standards, including the insertion of needles through clothes. Current acupuncture regulations, both international (WHO 1999) and local (AHW 2005), precisely detail protocols intended to maximize the safety of acupuncture practice, including procedures for sterilization and needling in the area of organs, but it is unknown what regulations were in place at the times and places of these AEs. The case of nerve impairment may have been due to a practice that was common in Japanese acupuncture, deliberately breaking needles and permanently embedding them in the body. Although this practice was discouraged in 1976, Yamashita et al. identified at least nine cases that occurred after this time (Yamashita 2001). The events we classified as mild overlap with categories that other authors have called 'harmless', 'non-serious', or 'unavoidable'.

The incidence of mild AEs from all treatment and control arms was calculated for studies of needle acupuncture that reported occurrence of harm. For the RCTs, the incidence was 32/196 patients (16.3%; 95% CI (11.2–21.5)) and 32/1999 sessions (1.6%; 95% CI (1.1–2.2)), while that obtained from the three usable cohort studies was 71/1131 patients (6.3%; 95% CI (4.9–7.7)) or 71/11630 sessions (0.61%; 95% CI (0.47–0.75)). Combining the AEs from both designs gives an overall incidence of mild AEs of 103/1327 patients (7.8%; 95% CI (6.3–9.2)) or 103/13629 sessions (0.76%; 95% CI (0.61–0.90)).

The report by Jindal et al. presented an overall AE incidence of 1.6/100 sessions. This calculation combined needle acupuncture (needle alone or with electric current), laser acupuncture, and injection of solution at acu-points. If we separate these three forms of acu-point stimulation and include only those arms that used acu-point stimulation as either treatment or control, we have AE values of 29/1163 sessions (2.5%; 95% CI (1.6–3.4)) for needle acupuncture, 0/449 sessions (0%) for laser acupuncture, and 0/93 sessions (0%) for acu-point injection, respectively. Using number of patients as the denominator, we come up with an AE incidence for needle acupuncture of 29/298 patients (9.7%; 95% CI (6.4–13.1)), for laser acupuncture of 0/180 patients (0%), and for acu-point injection of 0/93 patients (0%). The lack of AEs occurring in laser acupuncture and acu-point injection may be due, in part, to inherent differences between the three procedures. If we consider the RCTs of needle acupuncture alone, in order to compare the results of Jindal et al. with our SR, their determination of AEs, at 9.7% of patients is significantly lower than ours, at 16.3% of patients ($p=0.036$).

The methods used by Jindal et al. differ from ours in three key ways. First, the authors restricted their included studies to RCTs, second, they searched for efficacy studies and subsequently screened for mention of safety, and third, they included studies that did not report harms (either those that made no mention of harms or reports that stated that no harm occurred). We will address the methodological implications of each of these differences in turn.

Regarding the types of included studies, we chose to examine all sources of information, RCTs as well as case reports and observational studies, which are

known to be more useful in detecting AEs, especially long term or rare AEs, than are RCTs (Ioannidis 2004, Tang 1999). Case reports, in turn, often contain novel or serious AEs, as we found with our review, in that none of the case reports we found reported mild or moderate AEs. In reviews that are hypothesis testing or proving, such as in determining precise incidence of a readily detectable AE, already known to occur in relation to a certain intervention (i.e. fainting in adult acupuncture), restriction to controlled studies that limit bias, such as RCTs, may be warranted and recommended. In reviews that are hypothesis generating, such as in identifying AEs that may occur in relation to a new application of an intervention, (i.e. studies of acupuncture safety in children), use of all study designs may be needed in order to identify a broad range of potential events (i.e. those occurring in the short and long term, frequent or rare, mild or serious). The goal of our review was hypothesis generating and as such, we included all study designs.

Our search was designed to directly identify reports of harm, picking up terms for safety contained in titles and abstracts, and may have missed studies that assessed harm but did not make such reference in either of these places. The CONSORT statement for RCT abstracts recommends that important AEs or side-effects be included in abstracts (Hopewell 2008), but we would further recommend that if safety was assessed in any way, regardless if harm was detected or not, that general terms reflecting this assessment, such as *safety, adverse event, side effect,* or *harm*, be included in the abstract in order that searches for general terms may be more effective, and that this apply regardless of study design. The text should then go on to report either the detected harm or to report that no harm was detected.

Of note, during recalculation of the values in Jindal et al., we removed 80 patients/sessions from the study of electroacupuncture by Rusy et al., as this publication did not make any mention of safety or either the presence or absence of AEs and no mention of obtaining further information from the authors was made (Rusy 2002). This raises as important caution for safety review authors in

that the absence of mention of AEs is not the same as the absence of AEs (Loke 2007).

We also chose to assign a degree of association between the acupuncture treatments and AE, which resulted in the removal of one AE from our tally, while Jindal et al. included it in their count. This AE, unplanned overnight hospitalization for emesis following dental surgery under general anaesthesia, occurred at the same or higher frequency in the two control groups (ondansetron IV versus saline IV) and was judged by our reviewers as unlikely to have been due to the acupuncture (Somri 2001).

It is difficult to know the extent to which our results accurately represent the true AE incidence. Figure 3.2 demonstrates the complexity of collecting comprehensive information on AEs.

True known incidence of AEs may be represented by A+C+E+G/B+D+F+H, however, studies that fail to publish their results or report AE information cannot be counted, thus we are restricted to A+C/B+D, or A/B+D, since C = 0, as our best estimate. This estimate is influence by the assumptions made, including:

a) if we assume that only the publishing information on occurrence of AEs is true, our estimate would be A/B+D, since C = 0;
b) if we assume that no mention of AE = no occurrence of AE, then, based on published information, incidence = A/B+D+F, since E=0

In cases where AEs are rare, unpublished, or unreported data would impact the estimate by increasing the denominator much more than the numerator, thus reducing the estimate. In cases where AEs are common, inclusion of additional information would impact the estimate by increasing both the numerator and denominator. Less overall impact on the estimate may be observed since the relative difference between numerator and denominator would be lower than in the previous example.

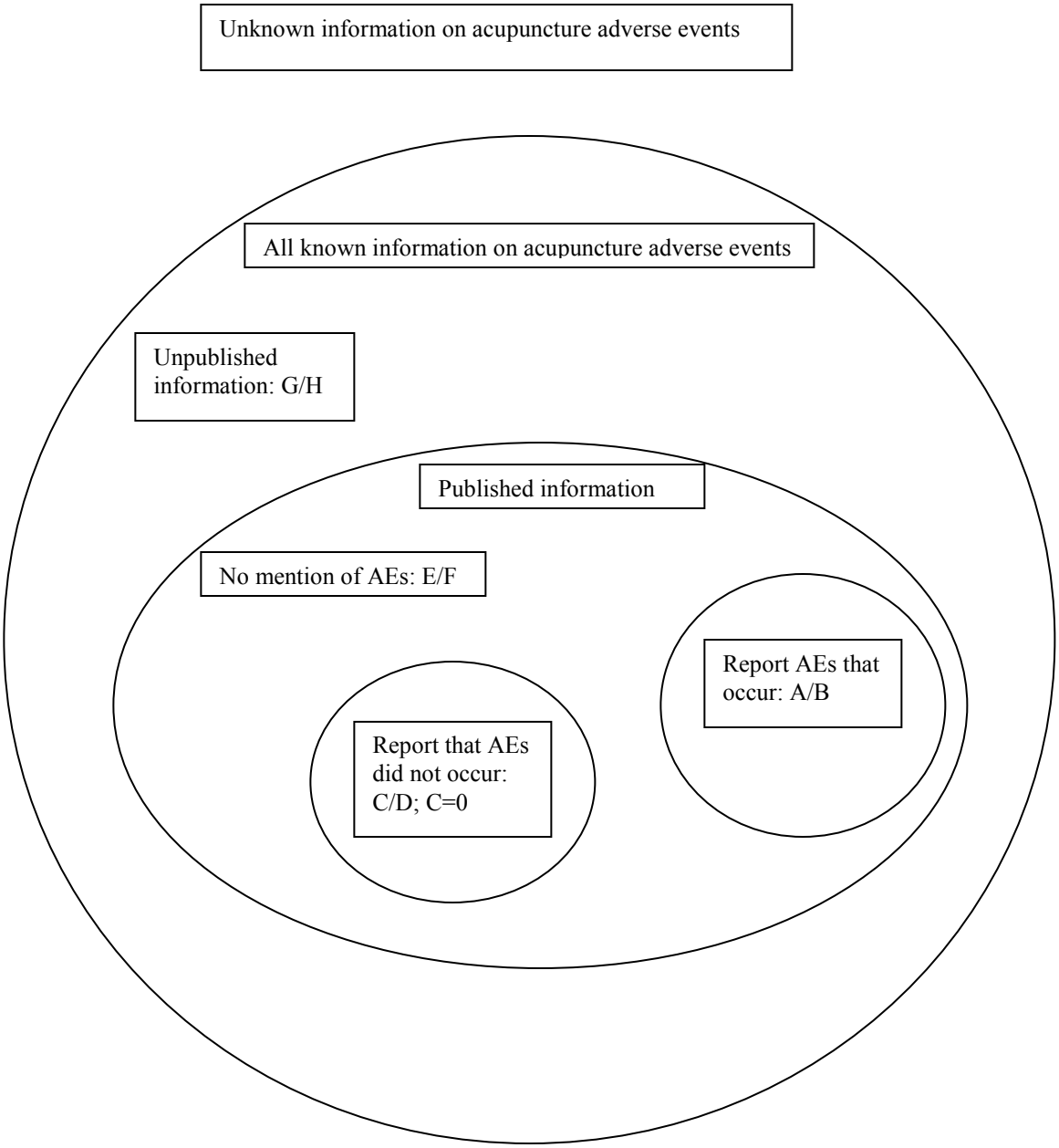

Figure 3.2: Inter-relationship of Reports of Adverse Events
Numerators reflect identified adverse events while denominators reflect populations in which the AEs occurred. Studies that report harms = A/B; studies that report occurrence of no harm = C/D; studies that do not mention harm = E/F; unpublished information on harm = G/H

At present, review authors are limited to the current body of literature and related conduct and reporting standards, thus caution is required in collecting, summarizing, and publishing information about AEs. Numerous research guidelines, including CONSORT statements (Boutron 2008, Fei 2008, Ioannidis 2004, Moher 2001, Zwarenstein 2008) are under varying levels of development and enforcement. The potential influence of CONSORT guidelines on publishing of AEs (i.e. restriction by journals on studies that do not comply with conduct or reporting), may impact most the values for E and F. In the ideal situation where all research studies are identifiable, (i.e. through the use of registries) the impact would be seen most through the values for G and H (Figure 3.2).

Regardless of their methodological differences, the incidence of AEs in the two sets of pediatric-specific results are much lower than that reported for similar events in adults – 53.9% (MacPherson 2005). This may be due, in part to the larger number of included patients (9408 compared to 1349 and 651), as well as study design, in that the adult data were collected during a prospective practice survey. In an editorial published a decade ago, MacPherson strongly encouraged the conduct of prospective practice surveys as a way of gathering the strongest safety evidence, overcoming limitations of both retrospective surveys and literature reviews (MacPherson 1999). Large scale prospective practice-based surveys have since been carried our in multiple countries, on several different styles of acupuncture, leading to convincing and reassuring safety information in adults. Repetition of this work in children would go far in closing this gap in pediatric safety knowledge and likely result in a more convincing estimate of risk of pediatric AEs.

An additional limitation of this study was the restriction of searches to conventional English-language databases, due to logistical considerations. Searches of non-English databases may have yielded further information. In some countries, international access to local literature may be difficult because papers may not be indexed in conventional databases and because access to local journals may be restricted. For example, in their review of the Japanese acupuncture safety literature, Yamashita et al. determined that out of the 89 articles they found, 70

were not listed in PubMed. In some cases, as in Japan, authors are collecting and publishing this local information in more readily available forms (Yamashita 2001). Others are collecting and synthesizing data from their own studies (Leung 2009).

3.5 Conclusions

Evaluation of the current pediatric literature identified few serious AEs, however, the small number of participants in the included studies hampers our ability to draw conclusions regarding the overall safety of pediatric acupuncture and to generalize to other populations. Based on the available data, we determined the incidence of mild AEs, occurring in needle acupuncture study arms, to be 7.8/100 patients (95% CI 6.4–9.2) or 0.76/100 sessions (95% CI 0.61–0.90). Estimates of overall risk of AEs in adult acupuncture, including serious AEs, have been possible due to the conduct of large prospective studies. The current pediatric acupuncture safety literature is limited to case reports and small studies or the inclusion of small numbers of children in predominantly adult studies. In order to produce convincing risk estimates for pediatric acupuncture, prospective large-scale pediatric studies are needed. With the increasing popularity of pediatric acupuncture, reliable information about its safety is urgently needed.

3.6 Reference List

Afari N, Buchwald D. Chronic fatigue syndrome: A review. *American Journal of Psychiatry.* 2003;160:221-236.

Alberta Health and Wellness. *Alberta Standards of Competencies and Practice for Acupuncturists*. Edmonton, AB: Alberta Health and Wellness, 2005.

Barnes PM, Bloom B, Nahin RL. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. *National Health Statistics Reports*. 2008;12.

Berman B, Sawyers J, Ezzo J. The evidence for acupuncture as a treatment for rheumatologic conditions. *Rheumatic Diseases Clinics of North America.* 2000;26(1):103-115.

Birch S. Clinical research on acupuncture: Part 1. What have reviews of the efficacy and safety of acupuncture told us so far? *Journal of Alternative and Complementary Medicine.* 2004;10(3):468-480.

Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Methods and processes of the CONSORT group: example of an extension for trials assessing nonpharmacologic treatments. *Annals of Internal Medicine.* 2008;148:6066.

Buchta RM. An unusual cause of petechiae. *American Journal of Diseases of Children*. 1972;123(6):613.

British Medical Association. *Acupuncture: Efficacy, Safety and Practice*. Amsteldijk, The Netherlands: Harwood Academic Publishers, 2000.

Campbell A. Acupuncture prolongs migraine attack. *Acupuncture in Medicine.* 1999;17(1):71.

Carette MF, Mayaud C, Houacine S, Milleron B, Toty L, Akoun G. Treatment of an asthmatic crisis by acupuncture. Probable role in the onset of pneumothorax with development to status asthmaticus. *Revue de Pneumologie Clinique*. 1984;40(1):69-70.

Chen FP, Hwang SJ, Lee HP, Yang HY, Chung C. Clinical study of syncope during acupuncture treatment. Acupuncture & Electro-therapeutics Research. 1990;15(2):107-119.

Cioppa FJ. Clinical evaluation of acupuncture in 129 patients. *Diseases of the Nervous System*. 1976;37(11):639-643.

Dincer F, Linde K. Sham interventions in randomized clinical trials of acupuncture – a review. *Complementary Therapies in Medicine.* 2003;11:235-242.

Egger M, Davey Smith G, Schneider M. Systematic reviews of observational studies In: *Systematic Reviews in Health Care: Meta-analysis in Context***,** M. Egger, G. Smith, and D. Altman Eds. London UK: BMJ Books, 2001 p211-213.

Endres HG, Molsberger A, Lungenhausen M, Trampisch HJ. An internal standard for verifying the accuracy of serious adverse event reporting: the example of an acupuncture study of 190,924 patients. *European Journal of Medical Research*. 2004 Dec 22;9(12):545-551.

Ernst G, Strzyz H, Hagmeister H. Incidence of adverse effects during acupuncture therapy – a multicentre survey. *Complementary Therapies in Medicine*. 2003;11(2):93-97.

Fei YT, Liu JP. Improving the quality of reporting Chinese herbal medicine trials: an elaborated checklist. *Zhong Xi Yi Jie He Xue Bao.* 2008;6(3):233-238.

Flaws R. *Alternative Medicine: The Definitive Guide*. Fife, WA: Future Medicine Publishing, 1993 p450-456.

Fuller JA. Letter: Acupuncture. *Medical Journal of Australia*. 1974 Aug 31;2(9):340-341.

Gold JI, Nicolaour CD, Belmont KA, Katz AR, Benaron DM, Yu W. Pediatric acupuncture: a review of clinical research. *eCAM.* 2009;6(4):429-439

Health Canada. *Guidelines for Reporting Adverse Reactions to Marketed Drugs.* 2001. www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2001-guide-ldir_indust/index-eng.php (Accessed Sept 15, 2009).

Hopewell S, Clarke M, Moher M, Wager E, Middleton P, Altman DG et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet*. 2008: DOI:10.1016/S0140-6736(07)61835-2.

Ioannidis J, Evans S, Gotzsche P, O'Neill R, Altman D, Schulz K et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine*. 2004;141:781-788.

Ishibe M, Inoue M, Saitou K. Septic arthritis of a lumbar facet joint due to pyonex. *Archives of Orthopaedic and Trauma Surgery*. 2001;121:90-92.

Jindal V, Ge A, Mansky P. Safety and efficacy of acupuncture in children: a review of the evidence. *Journal of Pediatric Hematology/Oncology*. 2008;30(6):431-442.

Kaptchuk T. Acupuncture: theory, efficacy and practice. *Annals of Internal Medicine.* 2002;136:374-383.

Kemper KJ, Sarah R, Silver-Highfield E, Xiarhos E, Barnes L, Berde C. On Pins and Needles? Pediatric pain patients' experience with acupuncture. *Pediatrics.* 2000;105(4):941-947.

Lau SM, Chou CT, Huang CM. Unilateral sacroiliitis as an unusual complication of acupuncture. *Clinical Rheumatology*. 1998;17:357-358.

Leggett Tait, P, Brooks L, Harstall C. *Acupuncture: evidence from systematic reviews and meta-analyses*. Edmonton, AB: Alberta Heritage Foundation for Medical Research Publishing, 2002.

Leung PC, Zhang L. Complications and adverse events in Chinese trials of acupuncture. *Acupuncture in Medicine*. 2008;26(2):121-122.

Leung PC, Zhang L, Cheng KF. Acupuncture: complications are preventable not adverse events. *Chinese Journal of Integrative Medicine*. 2009;15(3):229-232.

Lewith G, Machin D. On the evaluation of the clinical effects of acupuncture. *Pain.* 1983;16:111-127.

Liu C, Wang Y. 81 Cases of Paralytic Strabismus Treated with Acupuncture. *Journal of Traditional Chinese Medicine.* 1993;13(2):101-102.

Loh L, Nathan PW, Schott GD, Zilkha KJ. Acupuncture versus medical treatment for migraine and muscle tension headaches. *Journal of Neurology, Neurosurgery and Psychiatry*. 1984;47(4):333-337.

Loke Y, Price D, Herxheimer A et al. Systematic reviews of adverse effects: framework for a structured approach. BMC Medical Research Methodology. 2007;7(32):doi:10.1186/1471-2288-7-32.

MacPherson H. Fatal and adverse events from acupuncture: allegation, evidence, and the implications. *Journal of Alternative and Complementary Medicine*. 1999;5(1):47-56.

MacPherson H, Thomas K. Short term reactions to acupuncture – a cross sectional survey of patient reports. *Acupuncture in Medicine.* 2005;23(3):112-120.

MacPherson H, Thomas K, Walters S, Fitter M. A prospective survey of adverse events and treatment reactions following 34,000 consultations with professional acupuncturists. *Acupuncture in Medicine*. 2001;19(2):93-102.

Mayer D. Acupuncture: an evidence-based review of the clinical literature. *Annual Reviews in Medicine.* 2000;51:49-63.

Melchart D, Hager S, Weidenhammer W, Liao J, Liu Y, Linde K. Die erhubung von 'Nebenwirkungen' und begleitsymptomen bei akupunktubehanglung - eine pilotstudie *Akupunktur- Theorie und Praxis*. 1998;26:87-92.

Melchart D, Liao J, Hager S. *Projektbericht 1994 uber die Eerste Deutsche klinik fur Traditionelle Chinesischen Medizin Kotzting*. Munich: TCM Klinik Kotzting, 1995.

Melchart D, Liao J, Hager S. *Projektbericht 1995 uber die Erste Deutsche klinik fur Traditionelle Chinesischen Medizin Kotzting*. Munich: TCM Klinik Kotzting, 1996.

Melchart D, Weidenhammer W, Streng A, Reitmayr S, Hoppe A, Ernst E et al. Prospective investigation of adverse effects of acupuncture in 97 733 patients. *Archives of Internal Medicine*. 2004;164(1):104-105.

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet.* 2001;357(9263):1191-1194.

National Cancer Institute (NCI). *Grading: General Characteristics of the CTCAE Grading (Severity) Scale.* 2006. www.webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/welcome_to_ctcae.htm (Accessed Sept 15, 2009).

National Institutes of Health (NIH). *Acupuncture. NIH Consensus Statement*. 1997;15(5):1-34.

Ng DK, Chow PY, Ming SP, Hong SH, Lau S, Tse D et al. A double-blind, randomized, placebo-controlled trial of acupuncture for the treatment of childhood persistent allergic rhinitis. *Pediatrics.* 2004;114(5):1242-1247.

Odsberg A, Schill U, Haker E. Acupuncture treatment: side effects and complications reported by Swedish physiotherapists. *Complementary Therapies in Medicine*. 2001;9(1):17-20.

Oosthuysen WT, Berlyn PJ. Witchdoctor acupuncture. *South African Medical Journal*. 1979;21;56(3):86.

Reindl TK, Geilen W, Hartmann R, Wiebelitz KR, Kan G, Wilhelm I et al. Acupuncture against chemotherapy-induced nausea and vomiting in pediatric

oncology - Interim results of a multicenter crossover study. *Supportive Care in Cancer*. 2006;14(2):172-176.

Rusy LM, Hoffman GM, Weisman SJ. Electroacupuncture prophylaxis of postoperative nausea and vomiting following pediatric tonsillectomy with or without adenoidectomy. *Anesthesiology*. 2002;96:300-305.

Sanchez Araujo, M. Does the choice of placebo determine the results of clinical studies on acupuncture? *Forschende Komplementarmedizin.* 1998;5(suppl 1):8-11.

Sasaki H, Abe H, Iwasaki Y, Tsuru M, Itoh T. Direct spinal cord and root injury caused by acupuncture--report of 2 cases. *No Shinkei Geka.* 1984;12(10):1219-1223.

Shenkman Z, Holzman R, Kim C, Ferrari L, DiCanzio J, Highfield E, Van Keuren K, Kaptchuk T, Kenna M, Berde C, Rockoff M. Acupressure-acupuncture antiemetic prophylaxis in children undergoing tonsillectomy. *Anesthesiology*. 1999;90(5):1311-1316.

Somri M, Vaida SJ, Sabo E, Yassain G, Gankin I, Gaitini LA. Acupuncutre versus ondansetron in the prevention of postoperative vomiting: A study of children undergoing dental surgery. *Anaesthesia*. 2001;56:927-932.

Statistics Canada. Health Report: use of alternative health care. *The Daily.* 2004;16(2).

Sun JG, Ko CH, Wong V, Sun XR. Randomised control trial of tongue acupuncture versus sham acupuncture in improving functional outcome in cerebral palsy. *Journal of Neurology, Neurosurgery and Psychiatry*. 2004;75(7):1054-1057.

Tsao JC, Meldrum M, Bursch B, Jacob MC, Kim XC, Zeltzer LK. Treatment expectations for CAM interventions in pediatric chronic pain patients and their parents. *Evidence Based Complementary and Alternative Medicine*. 2005;2:521-527.

Umlauf R. Analysis of the main results of the activity of the acupucnture department of faculty hospital. *Acupuncture in Medicine*. 1988;5:16-18.

Vittecoq D, Mettetal JF, Rouzioux C, Bach JF, Bouchon JP. Acute HIV infection after acupuncture treatments. *New England Journal of Medicine*. 1989;26;320(4):250-251.

Weidenhammer W, Streng A, Linde K, Hoppe A, Melchart D. Acupuncture for chronic pain within the research program of 10 German Health Insurance Funds – basic results from an observational study. *Complementary Therapies in Medicine*. 2007;15:238-246.

White A. A cumulative review of the range and incidence of significant adverse events associated with acupuncture. *Acupuncture in Medicine.* 2004;22(3):122-133.

White A, Hayhoe S, Hart A, Ernst E. Survey of adverse events following acupuncture (SAFA): a prospective study of 32, 000 consultations. *Acupuncture in Medicine*. 2001;19(2):84-92.

Wong V, Sun JG, Wong W. Traditional Chinese medicine (tongue acupuncture) in children with drooling problems.see comment. *Pediatric Neurology*. 2001;25(1):47-54.

Wong VC, Sun JG, Yeung DW. Pilot study of efficacy of tongue and body acupuncture in children with visual impairment. *Journal of Child Neurology*. 2006;21(6):463-473.

World Health Organization (WHO). *Acupuncture: review and analysis of reports on controlled clinical trials*. Geneva, Switzerland: World Health Organization Publishing, 2002.

World Health Organization (WHO). *Guidelines on Basic Training and Safety in Acupuncture.* Geneva, Switzerland: World Health Organization Publishing, 1999.

Yamashita H, Tsukayama H. Safety of acupuncture practice in Japan: patient reactions, therapist negligence and error reduction strategies. *eCAM*. 2008;5(4):391-398.

Yamashita H, Tsukayama H, Hori N, Kimura T, Tanno Y. Incidence of adverse reactions associated with acupuncture. *Journal of Alternative and Complementary Medicine*. 2000;6(4):345-350.

Yamashita H, Tsukayama H, Sugishita C. Local adverse reactions commonly seen in Japanese-style medical acupuncture practice. *Clinical Acupuncture & Oriental Medicine.* 2001;2(3):132-137.

Yamashita H, Tsukayama H, Tanno Y, Nishijo K. Adverse events in acupuncture and moxibustion treatment: a six-year survey at a national clinic in Japan.see comment. *Journal of Alternative and Complementary Medicine*. 1999;5(3):229-236.

Ye TG. Death Caused by Acupuncture Needle Piercing the Heart. *Journal of Traditional Chinese Medicine*. 1956;8:433-434.

Yong D, Lim SH, Zhao CX, Cui SL, Zhang L, lee TL. Acupuncture treatment at Ang Mo Kio community hospital - a report on our initial experience. *Singapore Medical Journal*. 1999;40:260-264.

York University Centre for Health Studies. *Complementary and alternative practices and therapies – a Canadian overview.* Toronto, ON: York University Press, 1999.

Yudkin P, Livingstone R, Prasad K, Fuller A, Laurence M. Hay fever treatment in general practice: A randomised controlled trial comparing standardised western acupuncture with sham acupuncture. *Acupuncture in Medicine*. 1996;14(1):6-10.

Zeltzer LK, Tsao JC, Stelling C, Powers M, Levy S, Waterhouse M. A phase I study on the feasibility and acceptability of an acupuncture/hypnosis intervention for chronic pediatric pain. *Journal of Pain and Symptom Management*. 2002;24:437-446.

Zwarenstein M, Treweek S, Gagnier J, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ*. 2008;337:a2390 doi:10.1136/bml.a2390.

3.7 Appendices

Appendix 3.1: Acupuncture Safety Search Terms

(by database)

MEDLINE & Cochrane Database of SRs & HealthStar

exp acupuncture therapy/, acupuncture therap$, moxibustion/, moxibustion, acupuncture analgesia, acupuncture, ear, acupuncture point$, acupuncture, acupressure, press-needle$, de qi, laser puncture, acupoint, auriculotherap$, needling$, meridian$, reflexotherap$, Ryodoraku, acustimulation$, acupuncture standard$, acup$
AND
(ae or co or et), (Side or Advers$) adj3 (effect$ or affect$ or reaction$ or event$), (risk$ or harm$ or aetiolog$ or etiolog$ or cause or causation or causing or causal$ or complicat$), exp risk/, (risk-benefit adj5 (analy$ or ratio$ or assess$)), exp causality/, significant event, exp Safety/, safe$, aggravation$, consequences, injury, exp "Wounds and Injuries"/, case report$, side effect$, complication$, incident$, therapeutic safet$, symptom$, infect$, fatigue, (bleeding or haematoma), (bruise or ecchymosis or contusion), worsening.mp. or exacerbated symptom$, needle penetration$, drowsiness, dizziness, faint$, nause$, sweat$, headache$, neurological problem$, psychiatric problem$, allerg$, pain$, disorientat$, letharg$, vomit$, emesis, burn$, rash$, discomfort, malaise, itch$, erythema, fever, numbness, tingl$, chest pain$, vertigo, petechia, anxiety$, muscle tenderness, daz$, loss of appetite, blister$
AND
exp infant, newborn/, infant/, exp child, preschool/, child/, exp puberty/, minors/, adolescent/, (newborn$ or new-born$ or infan$ or baby$ or babies$ or preemie$ or prematur$), toddler$, (preschool$ or pre-school$), nursery school$, (kindergarten$ or kindergarden$), (child$ or kid or kids or boy$ or girl$), elementary school$, (schoolchild$ or "school child$"), (schoolage$ or school age$), ("junior high$" or "middle school$"), youth$, (teen$ or adolescen$ or juvenil$ or "young adult$" or pubert$ or underage$ or "under age$"), (pubescen$ or pre-pubescen$ or prepubescen$ or post-pubescen$ or postpubescen$), secondary school$, (high school$ or highschool$), exp Pediatrics/, pediatric$, paediatric

EMBASE & CENTRAL

acupuncture/, acupuncture, acupuncture therap$, (moxabustion or moxibustion), acupuncture analgesia, acupuncture, ear, acupuncture point$, acupuncture, acupressure, press-needle$, de qi, laser puncture, acupoint, auriculotherap$, needling$, meridian$, reflexotherap$, Ryodoraku, acustimulation$, acupuncture standard$, acup$

AND

((side or advers$) adj3 (effect$ or affect$ or reaction$ or event$)), (risk$ or harm$ or aetiolog$ or etiolog$ or cause or causation or causing or causal$), exp risk/, exp etiology/, (ae or co), exp epidemiology/, risk benefit analysis/, side effect/, causality, exp SAFETY/, safe$, aggravation$, consequence$, exp INJURY/, injury, exp case report/, case report, side effect$, complication$, incident$, therapeutic safet$, symptom$, infect$, fatigue, (bleeding or haematoma), (bruise or ecchymosis or contusion), worsening.mp. or exacerbated symptom$, needle penetration$, drowsiness, dizziness, faint$, nause$, sweat$, headache$, neurological problem$, psychiatric problem$, allerg$, pain$, disorientat$, letharg$, vomit$, emesis, burn$, rash$, discomfort, malaise, itch$, erythema, fever, numbness, tingl$, chest pain$, vertigo, petechia, anxiety$, muscle tenderness, daz$, loss of appetite, blister$

AND

exp Child/, exp Infant/, exp Adolescent/, exp Newborn/, exp Preschool Child/, (child$ or newborn$ or adolescen$ or infan$), (preschool$ or pre-school$), teen$, (kindergarten$ or kindergarden$), elementary school$, secondary school$, nursery school$, (high school$ or highschool$), youth$, (baby$ or babies$ or preemie$ or premature$), (schoolchild$ or "school child$"), (schoolage$ or school age$), toddler$, pubert$, (pre-pubescen$ or prepubescen$ or post-pubescen$ or postpubescen$), (kid or kids or boy$ or girl$), juvenile, exp PEDIATRICS/, pediatric$, paediatric

AMED

exp acupuncture/, acupuncture, acupressure/, acupressure, exp acupuncture therapy/, acupuncture therap$, moxibustion/, moxibustion, moxabustion, acupuncture analgesia, acupuncture, ear, acupuncture point$, press-needle$, de qi, laser puncture, acupoint, auriculotherap$, needling$, meridian$, reflexotherap$, Ryodoraku, acustimulation$, acupuncture standard$, acup$
AND
(ae or co or et), ((Side or Advers$) adj3 (effect$ or affect$ or reaction$ or event$)), (risk$ or harm$ or aetiolog$ or etiolog$ or cause or causation or causing or causal$ or complicat$), exp risk/, (risk-benefit adj5 (analy$ or ratio$ or assess$)), exp causality/, significant event, exp Safety/, safe$, aggravation$, consequences, injury, exp "Wounds and Injuries"/, exp treatment outcome/, exp Adverse Effects/, exp injuries/, case report$,
side effect$, complication$, incident$, therapeutic safet$, symptom$, infect$, fatigue, (bleeding or haematoma), (bruise or ecchymosis or contusion), worsening.mp. or exacerbated symptom$, needle penetration$, drowsiness, dizziness, faint$, nause$, sweat$, headache$, neurological problem$, psychiatric problem$, allerg$, pain$, disorientat$, letharg$, vomit$, emesis, burn$, rash$, discomfort, malaise, itch$, erythema, fever, numbness, tingl$, chest pain$, vertigo, petechia, anxiety$, muscle tenderness, daz$, loss of appetite, blister$
AND
exp infant, newborn/, infant/, exp child, preschool/, child/, exp puberty/, minors/, adolescent/, (newborn$ or new-born$ or infan$ or baby$ or babies$ or preemie$ or prematur$), toddler$, (preschool$ or pre-school$), nursery school$, (kindergarten$ or kindergarden$), (child$ or kid or kids or boy$ or girl$), elementary school$, (schoolchild$ or "school child$"), (schoolage$ or school age$), ("junior high$" or "middle school$"), youth$, (teen$ or adolescen$ or juvenil$ or "young adult$" or pubert$ or underage$ or "under age$"), (pubescen$ or pre-pubescen$ or prepubescen$ or post-pubescen$ or postpubescen$), secondary school$, (high school$ or highschool$), exp Pediatrics/, pediatric$, paediatric

Acubriefs

Adverse event OR adverse effect OR adverse reaction

CAMPAIN

Acupuncture OR acupoint OR moxibustion OR de qi OR meridian OR acupressure
AND
complication
AND
adolescent

Alternative Health Watch

(acupunctur*) or (MH "Acupuncture+") or (MM "Acupuncture Analgesia") or (MM " Acupuncture Points") or (MM "Acupuncture Anesthesia") or (MM "Acupuncturists") or (MM "Meridians") or (MM "Electroacupuncture") or (MM "Acupressure") or (acupunctur*) or (acupuncture therap*) or (moxibustion) or (acupuncture analgesia) or (ear acupuncture) or (acupuncture point*) or (acupressure) or (press-needle*) or (de qi) or (laser puncture) or (acupoint) or (ariculotherp*) or (needling*) or (merdian*) or (reflexotherap*) or (Ryodarku) or (acustimulation*) or (acupuncture standard*)

AND

(MH "Adverse Health Care Event+") or (MH "Adverse Drug Event+") or (MM "Iatrogenic Disease") or (MM "Medication Side Effects (Saba CCC)") or (Side effect) or (Side affect) or (side reaction) or (side event) or (Advers* effect) or (advers* affect) or (adverse resction) or (adverse event) or (risk*) or (harm*) or (aetiolog*) or (etiolog*) or (cause) or (causation) or (causing) or (causal*) or (complicat*) or (risk) or (risk-benefit analy*) or (risk-benefit ratio*) or (risk-benefit assess*) or (causality) or (significant event) or (safe*) or (aggravation*) or (consequences) or (injury) or (Wound) or (case report*) or (fatigue) or (bleeding) or (haematoma) or (bruis*) or (ecchymosis) or (contusion*) or (worsening symptom*) or (exacerbated symptom*) or (needle penetration*) or (drows*) or (dizz*) or (faint*) or (nausea*) or (sweat*) or (headache*) or (neurological problem*) or (psychiatric problem*) or (blister*) or (allerg*) or (pain*) or (disorientat*) or (letharg*) or (vomit*) or (emesis) or (burn*) or (rash*) or (discomfort) or (malaise) or (itch*) or (erythema) or (fever) or (numbness) or (tingl*) or (chest pain) or (vertigo) or (petechia) or (anxi*) or (muscle tenderness) or (daz*) or (loss of appetite)

AND

(pediatric) or (MM "Pediatrics+") or (infant) or (MM "Infant+") or (newborn) or (MM "Child+") or (child*) or (MH "Child, Preschool") or (Preschool*) or (pre-school) or (nursery school) or (kindergarden) or (kindergarten) or (puberty) or (MM "Puberty+") or (minors) or (MH "Minors (Legal)") or (adolescent) or (adolescence) or (MM "Adolescence+") or (newborn) or (new-born) or (MM "Infant, Newborn+") or (baby) or (preemie) or (premature) or (toddler) or (kid) or (boy) or (girl) or (elementary school) or (schoolchild*) or (school child*) or (schoolchild*) or (schoolage*) or (school age*) or (middle school) or (Junior high) or (MM "Students, Middle School") or (MM "Students, High School") or (MM "Students+") or (student) or (youth) or (teen*) or (juvenile*) or (underage*) or (under age*) or (pre-pubescen*) or (prepubescen*) or (post-pubescen*) or (postpubescen*) or (secondary school*) or (high school*)

CINAHL

(acupunctur*) or (MH "Acupuncture+") or (MM "Acupuncture Analgesia") or (MM " Acupuncture Points") or (MM "Acupuncture Anesthesia") or (MM "Acupuncturists") or (MM "Meridians") or (MM "Electroacupuncture") or (MM "Acupressure") or (acupunctur*) or (acupuncture therap*) or (moxibustion) or (acupuncture analgesia) or (ear acupuncture) or (acupuncture point*) or (acupressure) or (press-needle*) or (de qi) or (laser puncture) or (acupoint) or (ariculotherp*) or (needling*) or (merdian*) or (reflexotherap*) or (Ryodarku) or (acustimulation*) or (acupuncture standard*)

AND

(MH "Adverse Health Care Event+") or (MH "Adverse Drug Event+") or (MM "Iatrogenic Disease") or (MM "Medication Side Effects (Saba CCC)") or (Side effect) or (Side affect) or (side reaction) or (side event) or (Advers* effect) or (advers* affect) or (adverse reaction) or (adverse event) or (risk*) or (harm*) or (aetiolog*) or (etiolog*) or (cause) or (causation) or (causing) or (causal*) or (complicat*) or (risk) or (risk-benefit analy*) or (risk-benefit ratio*) or (risk-benefit assess*) or (causality) or (significant event) or (safe*) or (aggravation*) or (consequences) or (injury) or (Wound) or (case report*) or (fatigue) or (bleeding) or (haematoma) or (bruis*) or (ecchymosis) or (contusion*) or (worsening symptom*) or (exacerbated symptom*) or (needle penetration*) or (drows*) or (dizz*) or (faint*) or (nausea*) or (sweat*) or (headache*) or (neurological problem*) or (psychiatric problem*) or (blister*) or (allerg*) or (pain*) or (disorientat*) or (letharg*) or (vomit*) or (emesis) or (burn*) or (rash*) or (discomfort) or (malaise) or (itch*) or (erythema) or (fever) or (numbness) or (tingl*) or (chest pain) or (vertigo) or (petechia) or (anxi*) or (muscle tenderness) or (daz*) or (loss of appetite)

AND

(pediatric) or (MM "Pediatrics+") or (infant) or (MM "Infant+") or (newborn) or (MM "Child+") or (child*) or (MH "Child, Preschool") or (Preschool*) or (pre-school) or (nursery school) or (kindergarden) or (kindergarten) or (puberty) or (MM "Puberty+") or (minors) or (MH "Minors (Legal)") or (adolescent) or (adolescence) or (MM "Adolescence+") or (newborn) or (new-born) or (MM "Infant, Newborn+") or (baby) or (preemie) or (premature) or (toddler) or (kid) or (boy) or (girl) or (elementary school) or (schoolchild*) or (school child*) or (schoolchild*) or (schoolage*) or (school age*) or (middle school) or (Junior high) or (MM "Students, Middle School") or (MM "Students, High School") or (MM "Students+") or (student) or (youth) or (teen*) or (juvenile*) or (underage*) or (under age*) or (pre-pubescen*) or (prepubescen*) or (post-pubescen*) or (postpubescen*) or (secondary school*) or (high school*)

ICL

(acupunctur*) or (acupuncture therap*) or (moxibustion) or (acupuncture analgesia) or (ear acupuncture) or (acupuncture point*) or (acupressure) or (press-needle*) or (de qi) or (laser puncture) or (acupoint) or (ariculotherp*) or (needling*) or (merdian*) or (reflexotherap*) or (Ryodarku) or (acustimulation*) or (acupuncture standard*) **AND** Adverse event OR adverse effect OR adverse reaction OR caus* or complication* OR etiology OR harm OR risk* OR reaction OR safety OR side effect or (incident*) or (therapeutic safet*) or (symptom*) or (infect*) or (fatigue) or (bleeding) or (haematoma) or (bruis*) or (ecchymosis) or (contusion*) or (worsening symptom*) or (exacerbated symptom*) or (needle penetration*) or (drows*) or (dizz*) or (faint*) or (nausea*) or (sweat*) or (headache*) or (neurological problem*) or (psychiatric problem*) or (blister*) or (allerg*) or (pain*) or (disorientat*) or (letharg*) or (vomit*) or (emesis) or (burn*) or (rash*) or (discomfort) or (malaise) or (itch*) or (erythema) or (fever) or (numbness) or (tingl*) or (chest pain) or (vertigo) or (petechia) or (anxi*) or (muscle tenderness) or (daz*) or (loss of appetite) or (case report*) **AND** Infant* OR newborn* OR new-born* OR child* OR preschool* OR pre-school* OR puberty OR minors OR adolescent* OR baby* OR babies OR preemie* OR premature* OR toddler* OR nursery school* OR kindergarten* OR kindergarden* OR kid* OR boy* OR girl* OR elementary school* OR schoolchild* OR schoolage* OR school age* OR junior high* OR middle school* OR youth* OR teen* OR adolescent* OR juvenile* OR young adult* OR puberty* OR underage* OR pubescen* OR pre-pubescen* OR prepubescent* OR post-pubescen* OR postpubescen* OR secondary school* OR high school* OR highschool* OR Pediatric* OR paediatric

MANTIS

(acupunctur* OR acupuncture therap* OR moxibustion OR acupuncture analgesia OR ear acupuncture OR acupuncture point* OR acupressure OR press-needle* OR de qi OR laser puncture OR acupoint OR ariculotherp* OR needling* OR meridian* OR reflexotherap* OR Ryodarku OR acustimulation* OR acupuncture standard*)
AND
(adverse event OR adverse effect OR adverse reaction OR caus* or complication* OR etiology OR harm OR risk* OR reaction OR safety OR side effect OR fatigue OR bleeding OR haematoma OR bruis* OR ecchymosis OR contusion* OR worsening symptom* OR exacerbated symptom* OR needle penetration* OR drows* OR dizz* OR faint* OR nausea* OR sweat* OR headache* OR neurological problem* OR psychiatric problem* OR blister* OR allerg* OR pain* OR disorientat* OR letharg* OR vomit* OR emesis OR burn* OR rash* OR discomfort OR malaise OR itch* OR erythema OR fever OR numbness OR tingl* OR chest pain OR vertigo OR petechia OR anxi* OR muscle tenderness OR daz* OR loss of appetite OR case report*)
AND
(Infant* OR newborn* OR new-born* OR child* OR preschool* OR pre-school* OR puberty OR minors OR adolescent* OR baby* OR babies OR preemie* OR premature* OR toddler* OR nursery school* OR kindergarten* OR kindergarden* OR kid* OR boy* OR girl* OR elementary school* OR schoolchild* OR schoolage* OR school age* OR junior high* OR middle school* OR youth* OR teen* OR adolescent* OR juvenile* OR young adult* OR puberty* OR underage* OR pubescen* OR pre-pubescen* OR prepubescent* OR post-pubescen* OR postpubescen* OR secondary school* OR high school* OR highschool* OR pediatric* OR paediatric)

PsycInfo

exp acupuncture therapy/, acupuncture therap$, moxibustion/, moxibustion, acupuncture analgesia, acupuncture, ear, acupuncture point$, acupuncture, acupressure, press-needle$, de qi, laser puncture, acupoint, auriculotherap$, needling$, meridian$, reflexotherap$, Ryodoraku, acustimulation$, acupuncture standard$, acup$

AND

((side or advers$) adj3 (effect$ or affect$ or reaction$ or event$)), (risk$ or harm$ or aetiolog$ or etiolog$ or cause or causation or causing or causal$), exp risk/, exp etiology/, (ae or co), exp epidemiology/, risk benefit analysis/, side effect/, causality, exp SAFETY/, safe$, aggravation$, consequence$, exp INJURY/, injury, exp case report/, case report, side effect$, complication$, incident$, therapeutic safet$, symptom$, infect$, fatigue, (bleeding or haematoma), (bruise or ecchymosis or contusion), worsening.mp. or exacerbated symptom$, needle penetration$, drowsiness, dizziness, faint$, nause$, sweat$, headache$, neurological problem$, psychiatric problem$, allerg$, pain$, disorientat$, letharg$, vomit$, emesis, burn$, rash$, discomfort, malaise, itch$, erythema, fever, numbness, tingl$, chest pain$, vertigo, petechia, anxiety$, muscle tenderness, daz$, loss of appetite, blister$

AND

exp infant, newborn/, infant/, exp child, preschool/, child/, exp puberty/, minors/, adolescent/, (newborn$ or new-born$ or infan$ or baby$ or babies$ or preemie$ or prematur$), toddler$, (preschool$ or pre-school$), nursery school$, (kindergarten$ or kindergarden$), (child$ or kid or kids or boy$ or girl$), elementary school$, (schoolchild$ or "school child$"), (schoolage$ or school age$), ("junior high$" or "middle school$"), youth$, (teen$ or adolescen$ or juvenil$ or "young adult$" or pubert$ or underage$ or "under age$"), (pubescen$ or pre-pubescen$ or prepubescen$ or post-pubescen$ or postpubescen$), secondary school$, (high school$ or highschool$), exp Pediatrics/, pediatric$, paediatric

PubMed

(acupunctur*) or (acupuncture therap*) or (moxibustion) or (acupuncture analgesia) or (ear acupuncture) or (acupuncture point*) or (acupressure) or (press-needle*) or (de qi) or (laser puncture) or (acupoint) or (ariculotherp*) or (needling*) or (merdian*) or (reflexotherap*) or (Ryodarku) or (acustimulation*) or (acupuncture standard*) **AND** Adverse event OR adverse effect OR adverse reaction OR caus* or complication* OR etiology OR harm OR risk* OR reaction OR safety OR side effect or significant event or or injur* OR (Side affect) or (side reaction) or (side event) or (Advers* effect) or (advers* affect) or (adverse resction) or (adverse event) or (risk*) or (harm*) or (aetiolog*) or (etiolog*) or (cause) or (causation) or (causing) or (causal*) or (complicat*) or (risk) or (risk-benefit analy*) or (risk-benefit ratio*) or (risk-benefit assess*) or (causality) or (significant event) or (safe*) or (aggravation*) or (consequences) or (injury) or (Wound) or (case report*) **AND** newborn* OR new-born* OR child* OR preschool* OR pre-school* OR puberty OR minors OR adolescent* OR baby* OR babies OR preemie* OR premature* OR toddler* OR nursery school* OR kindergarten* OR kindergarden* OR kid* OR boy* OR girl* OR elementary school* OR schoolchild* OR schoolage* OR school age* OR junior high* OR middle school* OR youth* OR teen* OR adolescent* OR juvenile* OR young adult* OR puberty* OR underage* OR pubescen* OR pre-pubescen* OR prepubescent* OR post-pubescen* OR postpubescen* OR secondary school* OR high school* OR highschool* OR Pediatric* OR paediatric

Scopus

((acupunctur*) or (acupuncture therap*) or (moxibustion) or (acupuncture analgesia) or (ear acupuncture) or (acupuncture point*) or (acupressure) or (press-needle*) or (de qi) or (laser puncture) or (acupoint) or (ariculotherp*) or (needling*) or (meridian*) or (reflexotherap*) or (Ryodarku) or (acustimulation*) or (acupuncture standard*))
AND
(adverse event OR adverse effect OR adverse reaction OR caus* or complication* OR etiology OR harm OR risk* OR reaction OR safety OR side effect or (fatigue) or (bleeding) or (haematoma) or (bruis*) or (ecchymosis) or (contusion*) or (worsening symptom*) or (exacerbated symptom*) or (needle penetration*) or (drows*) or (dizz*) or (faint*) or (nausea*) or (sweat*) or (headache*) or (neurological problem*) or (psychiatric problem*) or (blister*) or (allerg*) or (pain*) or (disorientat*) or (letharg*) or (vomit*) or (emesis) or (burn*) or (rash*) or (discomfort) or (malaise) or (itch*) or (erythema) or (fever) or (numbness) or (tingl*) or (chest pain) or (vertigo) or (petechia) or (anxi*) or (muscle tenderness) or (daz*) or (loss of appetite) or (case report*))
AND
(Infant* OR newborn* OR new-born* OR child* OR preschool* OR pre-school* OR puberty OR minors OR adolescent* OR baby* OR babies OR preemie* OR premature* OR toddler* OR nursery school* OR kindergarten* OR kindergarden* OR kid* OR boy* OR girl* OR elementary school* OR schoolchild* OR schoolage* OR school age* OR junior high* OR middle school* OR youth* OR teen* OR adolescent* OR juvenile* OR young adult* OR puberty* OR underage* OR pubescen* OR pre-pubescen* OR prepubescent* OR post-pubescen* OR postpubescen* OR secondary school* OR high school* OR highschool* OR Pediatric* OR paediatric)

Sports Discus

(acupunctur*) or (acupuncture therap*) or (moxibustion) or (acupuncture analgesia) or (ear acupuncture) or (acupuncture point*) or (acupressure) or (press-needle*) or (de qi) or (laser puncture) or (acupoint) or (ariculotherap*) or (needling*) or (meridian*) or (reflexotherap*) or (acustimulation*) or (acupuncture standard*)
AND
DE "DRUGS -- Side effects" or Adverse event OR adverse effect OR adverse reaction OR caus* or complication* OR etiology OR harm OR risk* OR reaction OR safety OR side effect or (fatigue) or (bleeding) or (haematoma) or (bruis*) or (ecchymosis) or (contusion*) or (worsening symptom*) or (exacerbated symptom*) or (needle penetration*) or (drows*) or (dizz*) or (faint*) or (nausea*) or (sweat*) or (headache*) or (neurological problem*) or (psychiatric problem*) or (blister*) or (allerg*) or (pain*) or (disorientat*) or (letharg*) or (vomit*) or (emesis) or (burn*) or (rash*) or (discomfort) or (malaise) or (itch*) or (erythema) or (fever) or (numbness) or (tingl*) or (chest pain) or (vertigo) or (petechia) or (anxi*) or (muscle tenderness) or (daz*) or (loss of appetite) or (case report*)
AND
DE "PEDIATRIC sports medicine" OR DE "SPORTS injuries in children" or Infant* OR newborn* OR new-born* OR child* OR preschool* OR pre-school* OR puberty OR minors OR adolescent* OR baby* OR babies OR preemie* OR premature* OR toddler* OR nursery school* OR kindergarten* OR kindergarden* OR kid* OR boy* OR girl* OR elementary school* OR schoolchild* OR schoolage* OR school age* OR junior high* OR middle school* OR youth* OR teen* OR adolescent* OR juvenile* OR young adult* OR puberty* OR underage* OR pubescen* OR pre-pubescen* OR prepubescent* OR post-pubescen* OR postpubescen* OR secondary school* OR high school* OR highschool* OR Pediatric* OR paediatric

Web of Science

((acupunctur*) or (acupuncture therap*) or (moxibustion) or (acupuncture analgesia) or (ear acupuncture) or (acupuncture point*) or (acupressure) or (press-needle*) or (de qi) or (laser puncture) or (acupoint) or (ariculotherp*) or (needling*) or (merdian*) or (reflexotherap*) or (Ryodarku) or (acustimulation*) or (acupuncture standard*))
AND
(Adverse event OR adverse effect OR adverse reaction OR caus* or complication* OR etiology OR harm OR risk* OR reaction OR safety OR side effect or (incident*) or (therapeutic safet*) or (symptom*) or (infect*) or (fatigue) or (bleeding) or (haematoma) or (bruis*) or (ecchymosis) or (contusion*) or (worsening symptom*) or (exacerbated symptom*) or (needle penetration*) or (drows*) or (dizz*) or (faint*) or (nausea*) or (sweat*) or (headache*) or (neurological problem*) or (psychiatric problem*) or (blister*) or (allerg*) or (pain*) or (disorientat*) or (letharg*) or (vomit*) or (emesis) or (burn*) or (rash*) or (discomfort) or (malaise) or (itch*)) or ((erythema) or (fever) or (numbness) or (tingl*) or (chest pain) or (vertigo) or (petechia) or (anxi*) or (muscle tenderness) or (daz*) or (loss of appetite) or (case report*))
AND
(Infant* OR newborn* OR new-born* OR child* OR preschool* OR pre-school* OR puberty OR minors OR adolescent* OR baby* OR babies OR preemie* OR premature* OR toddler* OR nursery school* OR kindergarten* OR kindergarden* OR kid* OR boy* OR girl* OR elementary school* OR schoolchild* OR schoolage* OR school age* OR junior high* OR middle school* OR youth* OR teen* OR adolescent* OR juvenile* OR young adult* OR puberty* OR underage* OR pubescen* OR pre-pubescen* OR prepubescent* OR post-pubescen* OR postpubescen* OR secondary school* OR high school* OR highschool* OR Pediatric* OR paediatric)

Dissertation Abstracts

acupuncture or acupuncture therapy or moxibustion or acupuncture analgesia or ear acupuncture or acupuncture point or acupressure or press-needle or de qi or laser puncture or acupoint or ariculotherpy or needling or meridian or reflexotherapy or Ryodarku or acustimulation or acupuncture standard

Appendix 3.2: Common Terminology Criteria for Adverse Events (CTCAE) Scale: (NCI 2006)

Modified to group severe/undesirable, life-threatening/disabling, and death as Serious.

Mild (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance);

Moderate (minor, minimal intervention; local intervention; non-invasive intervention);

Serious
Severe and undesirable; life-threatening or disabling; death (experience or reaction is any untoward medical occurrence that at any dose results in significant symptoms requiring hospitalization or invasive intervention, transfusion, elective interventional radiological procedure, therapeutic endoscopy or operation; is complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis, life-threatening physiologic consequences, need for intensive care or emergent invasive procedure, emergent interventional radiological procedure, therapeutic endoscopy or operation or; results in death.

Appendix 3.3: Causality Assessment Algorithm (Health Canada 2001)

Modified: In order to be applicable to non-drug interventions, the term 'drug' was replaced with 'intervention'

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to intervention administration, and which cannot be explained by concurrent disease or other interventions. The response to withdrawal of the intervention (dechallenge) should be clinically plausible. The event must be definitive pharmacologically, phenomenologically or physiologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the intervention, unlikely to be attributed to concurrent disease or other interventions, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the intervention, but which could also be explained by concurrent disease or other interventions. Information on intervention withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to intervention administration which makes a causal relationship improbable, and in which other interventions or underlying disease provide plausible explanations.

Chapter 4: A Pragmatic Randomized Controlled Trial of Acupuncture Therapy for Infectious Mononucleosis

4.1 Introduction

Infectious mononucleosis (mono) is a common condition that carries a high illness burden, and for which there is no cure. Research on treatment has focused primarily on pharmaceuticals, including antivirals and steroids, however, clear benefit of these treatments has not been established (Andersson 1985, Andersson 1986, Andersson 1987, Bender 1967, Bolden 1972, Johansen 1997, Prout 1966, Roy 2004, Torre 1999, Tynell 1996, van der Horst 1991). Current treatment emphasizes symptom support and lifestyle changes (Candy 2005).

The use of complementary and alternative medicine (CAM), including acupuncture, is common in many patient populations (Lin 2004, Singer 2007, Spiegelblatt 1994). Although not yet formally documented, anecdotal evidence indicates that some patients with mono use acupuncture, both in the acute phase and to treat lingering symptoms.

Preliminary evidence suggests that acupuncture may be effective in treating viral infection. Studies of acupuncture effects on the immune system have been carried out in both animals and humans. Animal studies have demonstrated enhancement of splenic interferon gamma, interleukin-2, natural killer cell activity, and cortisol production. Studies in humans have demonstrated modulation of B and T cell populations that would favour antibody production, increases in CD3+, CD4+, and B cells, as well as neutrophil activity, natural killer cell activity, and phagocytosis of opsonized erythrocytes (Cabioglu 2008, Joos 2000, Karst 2003, Zan-Bar 2004).

Clinical trials of acupuncture have been conducted in a variety of populations. Medical conditions for which acupuncture has demonstrated positive immunomodulation include rheumatoid arthritis, allergic asthma, Hepatitis B, and chemotherapy induced leukopenia (Cabioglu 2008, Chen 1999, Joos 2000, Lu 2007, Lu 2009, Zan-Bar 2004). Clinical trials of infectious conditions for which improved clinical symptoms were reported include recurrent lower urinary tract

infection, hepatitis, HIV, and the common cold. Outcomes from these trials commonly demonstrated enhancement of the immune system and improvement of symptoms, however, fatigue was not specifically measured (Anastasi 1993, Aune 1997, Beal 2000, Chang 2007, Chen 1999, Kawakita 2004).

The term 'acupuncture' evokes images of acu-point stimulation, however, numerous other elements are considered integral to treatment including the consultation and diagnostic processes, patient and practitioner beliefs and expectations of acupuncture, practitioner skill, patient-practitioner relationship, physical setting and devices, protected time and attention from the practitioner, individualized treatment, and interaction of the aforementioned elements (Kaptchuk 2002, Paterson 2004, Paterson 2005, Thomas 2006, White 2001). Acupuncture is an example of a complex intervention. A complex intervention is one that is comprised of a number of separate elements considered essential to the proper functioning of the intervention (Blackwood 2006, MRC 2000). Other examples of complex health care interventions include physiotherapy, psychotherapy, chiropractic care, and occupational therapy. A study design that has been proposed as suitable for evaluating complex interventions is the pragmatic (or practical) clinical trial (PCT) (Blackwood 2006, Paterson 2005).

In contrast to a straightforward randomized controlled trial (RCT) in which a simple intervention (i.e. a new drug) is evaluated in comparison to a control intervention (i.e. a placebo or a drug already in use), a PCT can be used to evaluate a complex intervention or a system of care, often in comparison to another system of care. Unlike an RCT, which attempts to control all aspects of the trial, including the physical environment, in order to isolate the specific effects of the intervention, in a PCT, the intervention is offered according to normal practice and in a normal practice setting, in order to evaluate the overall effectiveness of the intervention in routine, everyday practice (MacPherson 2004). Characteristic features of PCTs include i) selection of clinically relevant interventions for comparison, ii) participation of a diverse study population, iii) recruitment of participants from heterogeneous practice settings, and iv) collection of a broad range of health outcomes (Tunis 2003).

Strengths and limitations of the PCT design are recognized. Strengths include i) usefulness in situations where use of placebo or sham controls is problematic, ii) deliverance of evidence of effectiveness in everyday clinical contexts and potential impact on decision-making, referral patterns, and clinical guidelines, iii) flexibility in treatment that may increase practitioner willingness to be involved in clinical trials, iv) lack of placebo treatment that may increase participant willingness to be involved in clinical trials, v) high generalizability and external validity. Limitations include i) inability to determine precisely what elements within a treatment process might have caused effect, ii) potential requirement of larger sample size due to heterogeneity of study population, and iii) lower internal validity due to lack of blinding (MacPherson 2004).

Blinding to intervention through the use of a placebo is common in pharmacological RCTs, however, blinding may be more difficult in RCTs assessing nonpharmacological interventions. A recent review of the feasibility of blinding in trials evaluating pharmacological and nonpharmacological treatments of hip and knee osteoarthritis reported that blinding of patients was considered possible less often with nonpharmacological interventions (42% versus 96%, $p<0.001$). When the nonpharmacological group was subdivided, patient blinding was deemed impossible for 22% of trials involving surgery, arthroscopy, and joint lavage and for 70% of trials involving rehabilitation, education, spa, and acupuncture (Boutron 2004). In cases where it is difficult or impossible to blind, every attempt to reduce ascertainment bias must be made. Techniques for doing so may include measuring and adjusting for baseline variables such as patient expectation, utilization of objective outcomes and blinded assessors, utilization of ITT analyses, and utilization of blinded analyses and interpretation. The implications of not blinding will be further explored in the methods section.

This RCT will investigate the feasibility of traditional Chinese acupuncture, applied as a complex intervention, in the treatment of mono.

4.2 Objectives

Primary

i) To determine the feasibility of conducting a clinical trial of acupuncture vs. conventional care (i.e. whole systems research) in mono patients in Edmonton, assessing: a) the characteristics of participating local physicians; b) the characteristics of participating subjects; and c) the acceptability of and compliance with protocols and outcome measurements.

Secondary

i) To inform design elements (e.g. to document the standard deviation of treatment effect, collect information regarding acupuncture treatment parameters) for a future RCT evaluating treatment effect; and

ii) To determine local incidence of mono.

4.3 Methods

Approval for this study was received from the University of Alberta Health Research Ethics Board.

4.3.1 Clinical Trial

Design

The design for this pilot study was a pragmatic parallel group randomized controlled clinical trial (PCT).

Intervention

Treatment

Needle acupuncture, as practiced according to the principles of TCM. Participants were assessed at the beginning of each session for individual patterns of symptom presentation and assigned a TCM-based diagnosis. Acu-points were selected based on the diagnosis and treatment principles. Solid, stainless steel, one-time-use, disposable needles were inserted to standard depths (i.e. 1-2 cm) and were left in place for 20 minutes. A sensation of de chi was sought and the

needles were manipulated as appropriate to the treatment principle. At each session the points selected reflected the individual patterns of symptom presentation and changed from session to session. In addition to providing acupuncture, other TCM therapies that were allowed included moxibustion, cupping, and diet and lifestyle recommendation, as these therapies are often part of acupuncture practice, serving to augment or support the acupuncture treatment principles, and it was our intention to mirror actual acupuncture practice as closely as possible. Due to regulatory restrictions, recommendation or provision of herbal products was not allowed. All aspects of treatment were recorded. Acupuncture was offered in conjunction with conventional care.

Practitioners

Acupuncture was available from four practitioners selected for this trial. Necessary credentials for selection included i) registration and licensing to practice TCM-style acupuncture in Alberta; ii) completion of acupuncture training through an approved, accredited facility; iii) minimum of 5 years of experience; iv) minimum of 500 hours of acupuncture practice; v) location of practice in Edmonton area; and vi) interest and availability to participate.

Control

Treatment

Conventional care alone acted as the comparison group. All medications and treatments were recorded.

Practitioners

The participants' primary physicians provided conventional care.

Recruitment

Three primary strategies to obtain physician participation in the trial were investigated: i) Monospot utilization data was used to identify physicians who were frequent users of the test, ii) anonymous patient localization data was used to

identify clinics where Monospot positive cases were frequently seen, and iii) diagnostic labs were asked to notify physicians of positive mono test results, asking them, in turn, to notify their patient of the study. Physicians who agreed to participate were provided manuals containing study forms. They were asked to notify eligible patients of the study and obtain consent, from those interested, to be contacted by the study coordinator, who would then proceed with enrolment procedures. In addition to patient recruitment by physicians, direct patient recruitment was attempted at several local post-secondary education institutions and busy walk-in clinics. Advertisements were placed in student health centres and clinics and circulated through student newsletters and list serves.

Participant Allocation

A web-based randomization service was used to assign eligible participants to intervention or control group, in a 2:1 ratio, at the time of enrolment. Unequal randomization has been suggested to be useful in clinical trials in which i) a substantial amount of previous experience relating to the control group exists, and ii) information regarding a new treatment is lacking (Avins 1998, Pocock 1979). This is the case for mono, where information regarding natural history and conventional care of mono is readily available (Candy 2002, Candy 2005, Johannsen 2005, Rea 2001), however, to our knowledge, acupuncture treatment of mono has not yet been documented through a clinical study. Utilization of a 2:1 ratio instead of 1:1 does not substantially decrease power. For example, with a significance level of 0.05, changing the proportion from 1:1 to 2:1 results in a small decrease in power from 95% to 92.5% (Pocock 1979). This ratio has been utilized in a variety of RCTs (Dumville 2006) including a recent acupuncture trial (MacPherson 2003).

Inclusion/Exclusion Criteria

Inclusion

i) aged 15-25 years, inclusive;

ii) resident of Edmonton and area;

iii) positive Monospot test and/or IgM to EBV capsid antigen;

iv) otherwise healthy;

v) onset of mono symptoms within 21 days prior to positive test result; and

vi) presence of fatigue at a level of 4 or more on the Chalder Fatigue Questionnaire (Chalder 1993). This level of fatigue has been recommended by the CFQ developer as the cut off point for identifying fatigue cases and was used as such in a recent mono trial (Candy 2004).

Exclusion

i) inability to communicate in English;

ii) lack of informed consent;

iii) unable to begin acupuncture within 21 days of positive test results;

iv) acupuncture use currently or in the past 3 months; and

v) currently under the care of a TCM practitioner.

Duration of Treatment Period

Acupuncture sessions were scheduled over a period of 6 weeks, with two sessions occurring in each of the first four weeks and one session occurring weekly for the remaining two weeks, for a total of 10 sessions. Additional sessions were available if considered necessary by the acupuncturist. Acupuncture research in other conditions has shown that studies with greater than six or eight sessions were significantly more likely to report positive results than those with fewer sessions (Ceccherelli 2000, Ezzo 2000). Such data is not available for viral infection, thus the number of sessions was based on previous acupuncture studies and expert recommendation, as well as feasibility and cost. Each session was expected to take up to 1 hour and took place in practitioners' offices.

Conventional care visits were scheduled by the participants as needed and conducted according to standard practice.

Outcome Measures

Primary

1. *Feasibility*: Feasibility and acceptability of study methods were assessed by collecting information such as success of physician and patient recruitment, protocol compliance, and completion of outcome measures.

2. *Fatigue*: Change in fatigue over 12 weeks following the start of treatment was measured using the Chalder Fatigue Questionnaire (CFQ) (Chalder 1993). Although the CFQ was developed for use in chronic fatigue syndrome populations, it was designed to measure fatigue not specifically related to chronic fatigue syndrome. This questionnaire consists of 11 questions assessing both physical and mental fatigue. It was tested for validity and reliability against the Clinical Interview Schedule – Revised fatigue section (Lewis 1992) in a British primary care population aged 18 to 45 (N=374). Reported test scores include Cronbach's Alpha of 0.88, sensitivity of 75.5, and specificity of 74.5. Additional validation information was provided through a recent study examining the properties of the Spanish version in a similar population; test scores confirmed the original results (Cho 2007). Although not validated specifically in mono, it was shown to be sensitive to change in mono patients aged 16 or older during a 2004 intervention trial (Candy 2004). The CFQ may be scored bimodally to determine cases of fatigue (considered to be greater than 3 out of a total score of 11) or continuously to determine overall fatigue score (total score 33).

Secondary

3. *Treatment Preference*: Participant treatment preference was ascertained before randomization by asking participants to select their preferred treatment (acupuncture, conventional care, no preference, or don't know). Responses were intended to be utilized to investigate the relationship between treatment preference, willingness to be randomized, and outcome.

4. *Belief/Expectation of Acupuncture*: The following question was asked in order to assess patient belief/expectation of acupuncture as a treatment. "Do you believe that acupuncture will reduce your fatigue?" This question was asked at the enrolment visit and scored on a 5-point likert scale where 1 = would definitely help, 2 = would probably help, 3 = don't know, 4 = would probably not help, 5 = would definitely not help (Linde 2007). Analyses were intended to investigate the relationship between levels of belief/expectation and outcome.

5. *Quality of Life*: Patient quality of life was assessed using the Medical Outcomes Study Short-Form Health Survey (SF-36). The SF-36 was developed to assess functional status and health related quality of life in populations aged 14 and older (Ware 1993). This questionnaire consists of 36 questions in 8 domains (physical functioning (PF), social functioning (SF), role - physical (RP), role – emotional (RE), mental health (MH), vitality (VT), pain (BP), and general health (GH) and can be completed in under 10 minutes. Validation studies have been conducted in many populations including general medical and primary care. Results of test scores include Cronbach's Alphas of 0.78 or over (PF-0.93, SF-0.85, RP-0.84, RE-0.83, MH-0.90, VT-0.87, BP-0.82, and GH-0.78) and test-retest values of less than 1 point change over a two-week interval. The SF-36 has been used in numerous observational and clinical studies including those with mono populations aged 16 and older (Buchwald 2000, Candy 2003, Candy 2004, Rea 2001, White 2004).

6. *Symptom Change*: Symptom change has been identified as the most likely assessment tool to be used by primary care physicians in the evaluation of mono (Wendy Vaudry, MD, Professor, Dept of Pediatrics, University of Alberta, Edmonton, AB & Dedra Buchwald, Professor, Dept of Medicine, Director, Chronic Fatigue Clinic, Harborview Medical Center, Seattle WA; personal communications)**.** In order to examine the effect of acupuncture on mono symptoms other than fatigue, changes in symptoms were captured using a checklist of common mono symptoms. Since a symptom checklist specific to mono has not yet been made available, we sought to design and test such a tool during this trial. Patients were asked how much each symptom bothered them

during the previous week. Symptoms were scored on a 5-point likert scale where 1 = not at all, 2 = a little bit, 3 = moderately, 4 = quite a bit, 5 = extremely. This language and scoring was chosen to be consistent with that contained in the SF-36. Specific symptoms were chosen based on previous publications (Johannsen 2005, Rea 2001).

7. *Treatment Details*: Evaluation, diagnosis and treatment provided or recommended were carefully documented. It was hoped that this data would provide information on progression of mono over time, conventional treatment recommendations and effects, as well as the effect of adding acupuncture as an adjunctive treatment. Collection of TCM diagnoses was hoped to provide information on syndrome classifications of mono as well as treatment strategies.

8. *Absence from School or Work*: Participants were asked to record school or work attendance.

9. *Medication Use*: Participants were asked to record use of any products or therapies during the trial.

10. *Acupuncture Effects*: Acupuncture effects, positive or negative, were collected by both patients and practitioners.

11. *Compliance, Withdrawal, Dropout*: Information regarding compliance with procedures and study completion was collected.

Method, Frequency, and Duration of Follow-up

Demographics

Consent information, demographic, and clinical information (i.e. gender, age, education level, socio-economic status, medical history, lab test results), and inclusion/exclusion data was collected on all eligible participants at the time of enrolment to the study and recorded on the appropriate forms. Signed consent was also obtained at this time.

Baseline Measures

Treatment preference and belief/expectation of acupuncture were collected on all eligible patients during the enrolment visit. Baseline completion of the CFQ, the SF-36, and the symptom checklist were collected at this time. Clinical measurements (i.e. hemoglobin level) and relevant medical history were obtained from physicians.

Follow-up Measures

Questionnaires: Participants were provided with data form packages as well as pre-addressed, stamped envelopes, which were returned by mail to the coordination centre weekly for 12 weeks, beginning the week following enrolment (control group) or the first acupuncture session. This package included the CFQ, SF-36, symptom checklist, absence from school/work forms, medication forms, and patient adverse event forms.

Treatment Details: Assessment and treatment details were collected at every appointment and recorded on the appropriate forms.

Adverse events: Adverse events were recorded on the appropriate Adverse Events Report Form and faxed to the coordination centre. All participants were provided with an emergency contact number as well as instructions regarding when to call. The senior investigator (SV) was notified of any serious adverse event (e.g. hospitalization) within 24 hours of occurrence. A three-member safety committee was notified within 48 hours of the occurrence of any serious adverse event and was empowered to stop the study prematurely should a safety concern emerge.

Feasibility: Feasibility information (i.e. physician recruitment rate, patient recruitment rate, completion of outcome measures, protocol compliance) was collected throughout the trial.

Analysis

Descriptive statistics were compiled on demographic and baseline data. Means and standard deviations were presented for normally distributed data while counts and frequencies were presented for categorical data. Descriptive statistics were also be used to examine data related to study feasibility and treatment parameters. The primary analysis was intended to be number of fatigue cases at week six. The CFQ was scored bimodally to identify fatigue cases (scores of over 3/11); between group differences were intended to be compared using logistic regression. CFQ scores were presented graphically as both scale and bimodal scores. Secondary analyses were to include fatigue cases at other time points, SF-36 scores, presence of additional symptoms, absence from school or work, use of medication, and treatment side effects (all presented weekly). SF-36 scores were presented graphically as total scores and as domain scores, with the data for each domain transformed to a 0-100 scale in order to facilitate comparisons between scales (Ware 2005). Binary outcomes were intended to be examined using logistic regression while continuous outcomes were intended to be analyzed using linear regression. Analysis of outcome data was to follow intention-to-treat principles. Data missing from repeated measures were to be handled using the Last Observation Carried Forward method. All statistical tests were two-sided and performed at the 0.05 level of significance. Analyses were carried out when all participants reached the end of the study (12 weeks).

Methodological Considerations

Numerous studies have examined the impact of elements of study design on treatment effect (Tables 4.1, 4.2, 4.3). These studies focused primarily on randomization, allocation concealment, and blinding (Balk 2002, Benson 2000, Chalmers 1983, Egger 2003, Ioannidis 2001, Juni 2002, Khan 1996, Kjaergard 2001, Kunz 1998, Moher 1998, Schulz 1995, Wood 2008), however, drawing conclusions regarding the relative impact of these elements on treatment effect is difficult due to the contradictory nature of the results; only approximately half of the studies for each element report statistically significant results.

Randomization (Table 4.1)

Seven studies examined the influence of randomization on treatment effect. Increases of 5%, 11%, 25%, and 51% were reported for lack of randomization or inadequate generation of allocation sequence, in four studies, however, only the 51% increase was statistically significant (Khan 1996, Kjaergard 2001, Moher 1998, Schulz 1995). The remaining studies reported their results as: increased frequency of significant outcomes from 8.8% to 58.1% (Chalmers 1983), good correlation between odds ratios (ORs) for non-randomized and randomized studies (Ioannidis 2001), and similar estimates of effect between non-randomized and randomized studies (Benson 2000).

Allocation Concealment (Table 4.2)

Eight studied examined the influence of allocation concealment on treatment effect (Balk 2002, Chalmers 1983, Egger 2003, Juni 2002, Khan 1996, Kjaergard 2001, Moher 1998, Schulz 1995). Increases of between 5% and 41% were reported for lack of or inadequate allocation concealment, with the increases of 21%, 25%, 37%, and 41% being statistically significant. The remaining study reported increased frequency of significant outcomes from 8.8% to 24.4% (Chalmers 1983).

Blinding (Table 4.3)

Seven studies examined the influence of double blinding on treatment effect. Increases of between 2% and 44% were reported for lack of double blinding, however, only the 12%, 17%, and 44% increases were statistically significant (Balk 2002, Egger 2003, Juni 2002, Khan 1996, Kjaergard 2001, Schulz 1995). One other study reported a non-significant decrease of 11% (Moher 1998).

Reasons for this apparent inconsisitency have been proposed and include differences in populations studied, differences in analytic techniques, differences in interpreting and applying assessment criteria, and heterogeneity of included studies (Kunz 1998, Wood 2008). A recent study by Wood et al. focused

specifically on the influence of subjective and objective outcomes by reanalyzing the trials contained in the studies by Egger, Kjaergard, and Schulz after first classifying the trials as having either subjective or objective outcomes. The authors demonstrated that while there was an increase in estimate of treatment effect of 25% for inadequate allocation concealment and 31% for lack of double blinding, this increase was observed only for subjective outcomes, while the effect on objective outcomes was minimal and non-significant (Wood 2008).

There was one study found that examined the impact of different types of blinding on treatment effect, including patient, caregiver, and outcome assessor blinding (Balk 2002). The authors reported that lack of patient or caregiver blinding decreased treatment effect while lack of outcome assessor or double blinding increased treatment effect, however, none of these results were statistically significant.

Table 4.1: Impact of Randomization on Estimate of Treatment Effect

Author; Date	Included Studies; MAs	Population	Outcome (objective, subjective, or both)	Effect
Chalmers; 1983	145 studies	Myocardial infarction	Objective	Frequency of significant outcomes: 58.1% (non-R); 8.8% (R); p<0.0001
Schulz; 1995	250 studies; 33 MAs	Pregnancy, childbirth	NR	Inadequate SG increased adjusted OR by 5% (**not sign**); adjusted OR=0.95; 95% CI (0.81-1.12); analysis restricted to adequately concealed studies resulted in increased estimate of effect of 25% (**not sign**); adjusted OR=0.75; 95% CI (0.55-1.02)
Khan; 1996	34 studies; 9 MAs	Fertility treatments	Objective	Inadequate SG increased adjusted OR by 5% (**not sign**); adjusted OR=1.05; 95% CI (0.29-3.76)
Moher; 1998	127 studies; 11 MAs	Various	Both, most objective	Inadequate SG increased OR by 11% (**not sign**); OR 0.89; 95% CI (0.67-1.20)
Benson; 2000	136 studies	Various	Both, most objective	Similar estimates of effect
Ioannidis; 2001	408 studies; 45 MAs	Various	Both, most objective	Good correlation between ORs for non-R and R studies (r=0.75)
Kjaergard; 2001	190 studies; 14 MAs	Various	Objective	Inadequate SG increased treatment effect by 51%; OR=0.49; 95% CI (0.30-0.81)

OR = odds ratio; NR = not recorded; NA = not applicable; MA = meta-analysis; R = randomized; non-R = non- randomized; SG = sequence generation; not sign = not statistically significant

Table 4.2: Impact of Allocation Concealment on Estimate of Treatment Effect

Author; Date	Included Studies; MAs	Population	Outcome (objective, subjective, or both)	Effect
Chalmers; 1983	145 studies	Myocardial infarction	Objective	Frequency of significant outcomes: 24.4% (non-concealed); 8.8% (concealed); (**not sign**); p=0.053
Schulz; 1995	250 studies; 33 MAs	Pregnancy, childbirth	NR	Inadequate AC increased adjusted OR by 41%; adjusted OR=0.59; 95% CI (0.48-0.73)
Khan; 1996	34 studies; 9 MAs	Fertility treatments	Objective	Inadequate AC increased adjusted OR by 27% (**not sign);** adjusted OR=1.27; 95% CI (0.43-3.74)
Moher; 1998	127 studies; 11 MAs	Various	Both, most objective	Inadequate AC increased OR by 37%; OR=0.63; 95% CI (0.45-0.88)
Kjaergard; 2001	190 studies; 14 MAs	Various	Objective	Inadequate AC increased treatment effect by 40% (**not sign**); OR=0.60; 95% CI (0.31-1.15)
Balk; 2002	276 studies; 26 MAs	Various	Both	Inadequate AC increased treatment effect 5% (**not sign**); OR=1.05; 95% CI (0.91-1.21)
Juni; 2002	NR	NR	NR	Inadequate AC increased treatment effect by 25%; OR=0.75; 95% CI (0.63-0.89)
Egger; 2003	304 studies; 39 MAs	Various	NR	Inadequate or unclear AC increased treatment effect by 21%; ratio of OR=0.79; 95% CI (0.70-0.89)

OR = odds ratio; NR = not recorded; NA = not applicable; MA = meta-analysis; AC = allocation concealment; not sign = not statistically significant

Table 4.3: Impact of Blinding on Estimate of Treatment Effect

Author; Date	Included Studies; MAs	Population	Outcome (objective, subjective, or both)	Effect
Schulz; 1995	250 studies; 33 MAs	Pregnancy, childbirth	NR	Lack of DB increased adjusted OR by 17%; adjusted OR=0.83; 95% CI (0.71-0.96)
Khan; 1996	34 studies; 9 MAs	Fertility treatments	Objective	Lack of DB increased adjusted OR by 42% (**not sign);** adjusted OR=1.42; 95% CI (0.69-2.92)
Moher; 1998	127 studies; 11 MAs	Various	Both, most objective	Lack of DB decreased OR by 11% (**not sign);** OR =1.11; 95% CI (0.76-1.63)
Kjaergard; 2001	190 studies; 14 MAs	Various	Objective	Lack of DB increased treatment effect by 44%**;** OR=0.56; 95% CI (0.33-0.98)
Balk; 2002	276 studies; 26 MAs	Various	Both	Lack of patient blinding decreased treatment effect by 5% (**not sign**); OR =0.95; 95% CI (0.70-1.13); lack of caregiver blinding decreased treatment effect 2% (**not sign);** OR=0.98; 95% CI (0.75-1.20); lack of outcome assessor blinding increased treatment effect 2% (**not sign);** OR=1.02; 95% CI (0.82-1.22); lack of DB increased treatment effect 2% (**not sign);** OR=1.02; 95% CI (0.79-1.24)
Juni; 2002	NR	NR	NR	Lack of DB increased OR by 12%; OR=0.88; 95% CI (0.78-0.99)
Egger; 2003	399 studies; 45 MAs	Various	NR	Lack of DB increased treatment effect by 12% (**not sign**); ratio of OR = 0.88; 95% CI (0.0.75-1.04)

OR = odds ratio; NR = not recorded; NA = not applicable; MA = meta-analysis; DB = double blinded; not sign = not statistically significant

Implications of not blinding

Potential effects of not blinding are recognized and may include ascertainment bias, which is the systematic distortion of results due to knowledge of treatment assignment (Jadad 1998). This knowledge has been suggested to affect response by influencing i) treatment expectations of unblinded patients (i.e. expectation of positive response by the treatment group versus expectation of negative response in the control group), ii) compliance and retention of participants, iii) attitudes of unblinded practitioners which may be transferred to patients and/or affect treatment administration, and iv) outcome assessment (Schulz 2002). These issues were addressed in the trial as follows. Participant belief and treatment expectation are considered part of a complex intervention and are not intended to be masked or diminished in this trial. Belief and expectation in the intervention were collected before randomization. Differences between groups were intended to be explored statistically and the effect on outcomes assessed and controlled for during analyses (Linde 2007, Torgerson 1996). Compliance and participant retention were monitored and included in examinations of feasibility. With respect to practitioner attitudes and behaviours, in complex interventions practitioner beliefs, attitudes and behaviours are considered key elements; this trial did not seek to change or control them. It was expected that both acupuncturists and conventional care physicians would act to maximize the effectiveness of their respective care protocols. Unblinded assessment of subjective outcomes such as pain and fatigue provide more opportunity for bias than do objective outcomes such as lab tests (Schulz 2002). Unfortunately there is currently no objective method to measure fatigue. Assessment of and comparison with additional outcomes such as functional measures were hoped to assist in evaluating the potential influence of bias in the fatigue outcome.

Reduction of other forms of bias were enhanced through meticulous randomization, allocation concealment, and blinding of data entry and analysis. Separation of functions performed by members of the research team may have also contributed to reduction of bias. For example, a research assistant who did

not have contact with trial participants received the completed, coded forms and entered the data in a blinded fashion. Similarly, data analysis and interpretation of study results occured blind to treatment group.

4.3.2 Infectious Mononucleosis Population Characteristics

Data retrieval

Laboratory data for the Capital Health Region (CHR) of central Alberta, Canada, was retrieved for the years 2003-2008 from the Laboratory Information System (LIS) repository through a request to the Regional Clinical Trials Coordinator for Alberta Health Services. This database contains all laboratory results originating from the centralized LIS and contains all Monospot tests from the CHR. The retrieval request was for all positive Monospot test results between inception of the database (April 2003) and July 2008. Additional information requested included patient gender, date of birth, date of test, collection location, and name of requesting physician. Data was summarized by year and duplicates removed, based on unique patient id codes. Data for any missing time periods were extrapolated from available data. Annual incidence rates were calculated using mid-year population values for the CHR, which were obtained from the Government of Alberta Health and Wellness Interactive Health Data Application (AHW). This database contains information on registered members of the Alberta Health Care Insurance Plan (ACHIP), which is a provincial component of the universal health care system in place in Canada. Based on comparison to census data obtained from the Government of Alberta for the same years, registered members of the AHCIP made up over 99% of the census population (Government of Alberta).

For this study, population values were obtained for all ages combined and for the 15-25 year old group alone.

Data analysis

Data was summarized using descriptive statistics, including counts, frequencies, means, and standard deviations. Age and temporal distributions were presented graphically. Comparison of counts between years was carried out using chi-square tests (i.e., proportions of all cases, cases by age group, and cases by gender). Temporal relationships (i.e., differences in number of cases per month between months and between years) were investigated through Poisson regression. Use of this analysis allowed us to examine differences in Monospot positive counts between months, while controlling for the effect of year and vice versa. The reference month chosen was April and the reference year, 2005. Likelihood ratio test was used for statistical inference.

4.4 Results

4.4.1 Clinical Trial

Between Jan 2006 and June 30, 2008, 2400 Monospot positive cases, aged 15-25 years, were detected in the CHR. Of these, 22% were seen in hospitals or emergency rooms, 26% in high volume walk in clinics such as MediCentres, and a further 5% in post-secondary education student health centres. The remaining 47% were seen primarily in private medical clinics (Table 4.4).

Table 4.4: Distribution of 15-25 Year Old Monospot Positive Cases in CHR Health Care Centres Jan 2006-July 2008

Site	Hospitals & Emergency Rooms	MediCentre & AllWell Sites	Post-Secondary Student Health Centre	Other*	Total Cases
Edmonton	301 (12.5%)	516 (21.3%)	113 (4.7%)	NR	
Non-Edmonton	233 (9.7%)	102 (4.2%)	NR	NR	
Total Cases	534 (22.2%)	618 (25.8%)	113 (4.7%)	1135 (47.3%)	2400 (100%)

NR = not recorded; Other* sites included private physician offices

Physician Recruitment

Physician recruitment strategies I and II were employed, however, the diagnostic lab declined to participate. Responses were received from 69 physicians; 16 agreed to participate while 53 declined. The two most common reasons for not participating were: not seeing enough mono patients (32=60.4%) and being too busy (18=34.0%). Two physicians withdrew at the start of the study because they felt they did not see enough mono patients. The 14 recruiting physicians consisted of eight males and six females. Six worked in walk-in clinics and eight worked in private offices. Based on the data for 2006-2008, the six recruiting walk-in clinics saw 9.1% of the total number of cases or 35.4% of the cases seen by all area MediCentres and AllWell clinics (approximately seven cases, in the age range under study, per month).

Patient Recruitment

Between Jan 21 and Dec 31, 2008, participating physicians identified 24 patients with confirmed mono, of which 17 met screening criteria and were informed of the study; three of the eligible patients (18%) consented to participate. Reasons for refusal included patient not being interested in research (10), patient not being interested in acupuncture (1), and patient being too busy to participate (3).

Direct patient advertising did not identify any further eligible patients.

The three consenting patients were recruited from two MediCentres. Two were enrolled in April and the third in May 2008; all three patients completed the study. All patients were females between the ages of 16-19. One was assigned to the control group (control) and two to the treatment group (Acu1 and Acu2). None of the three patients had experienced acupuncture before. Other baseline characteristics of the three patients are shown in table 4.5.

Table 4.5: Baseline Participant Characteristics

Characteristic		**Acupuncture N=2**	**Control N=1**
Patient Reference ID		Acu1, Acu2	Control
Gender: female		2	1
Age: years		18, 19	16
Diagnostic Blood Tests		Monospot alone	Monospot; IgM VCA
Ethnicity: Caucasian		2	1
Student status: yes		1	1
Number of people in residence		3, 2	4
Hemoglobin: (g/L)		149, 138	138
Days inactive between symptom start and baseline		4, 8	11
Days from symptom start to baseline		11, 8	12
CFQ Total Score	Bimodal	10, 8	10
	Scale	21, 21	22
SF-36 Total Score		97, 110	94
Symptoms/severity*			
Sore throat		4, 5	3
Swollen glands		4, 5	4
Fever		3, 4	1
Chills		3, 4	3
Rash		1, 2	1
Loss of appetite		4, 2	4
Muscle ache/pain		3, 3	2
Joint ache/pain		2, 3	2
Abdominal ache/pain		4, 1	2
Cough		4, 2	5
Nausea/upset stomach		4, 1	2
Vomiting		4, 1	2
Concurrent Medications			
Antibiotics		1	1
Analgesics			1
Steroids		1	
Other (birth control)		1	
Treatment preference**		3, 1	2
Belief in Acu***		3, 2	1

*1=not at all, 2=a little bit, 3=moderately, 4=quite a bit, 5=extremely;
**1=acupuncture, 2=conventional care, 3=no preference; ***1=definitely help, 2=probably help, 3=don't know, 4=probably won't help, 5=definitely won't help

Patient Treatment

Diagnosis and Treatment Parameters: Two patients received acupuncture treatment, both from the same practitioner, who was trained though an accredited traditional Chinese acupuncture program of 200 hours duration and who had 20 years of practical acupuncture experience.

At the first treatment session, Acu1 was diagnosed with deficiency of spleen Qi and excess heart heat, for which the following treatment principles were applied: tonify spleen Qi, clear heat, and enhance immune system. Acu2 was initially diagnosed with deficiency of kidney Qi, liver Qi stasis, and invasion of wind heat, for which the following treatment principles were applied: tonify kidney and spleen, clear wind heat, and sedate liver.

Acu1 received 9 sessions over a period of 5 weeks. A total of 140 (average 14/session) needles were used at 36 different points. Acu2 received 12 sessions, 8 twice weekly followed by 3 weekly sessions and a last session two weeks later. A total of 175 (average 14.6/session) needles were used at 33 different points.

Stainless steel 0.25 gauge needles of 25 and 40 mm were used. Insertion depths ranged between 3 and 33 mm. Needles were retained for approximately 20 minutes and stimulated primarily by rotation. Commonly treated points for Acu1 included: Spleen 6 and 10, Stomach 25 and 36, Large Intestine 11, and Heart 7. Commonly treated points for Acu2 included all those for Acu1 plus Governing Vessel 14, Gall Bladder 21, and Bladder 20 and 23 (Figure 4.1).

In addition to acupuncture, Acu1 received diet and lifestyle recommendations such as breathing, relaxation, and yoga, while Acu2 received cupping at acupuncture points (to intensify the action of the acupuncture needles) and diet recommendations.

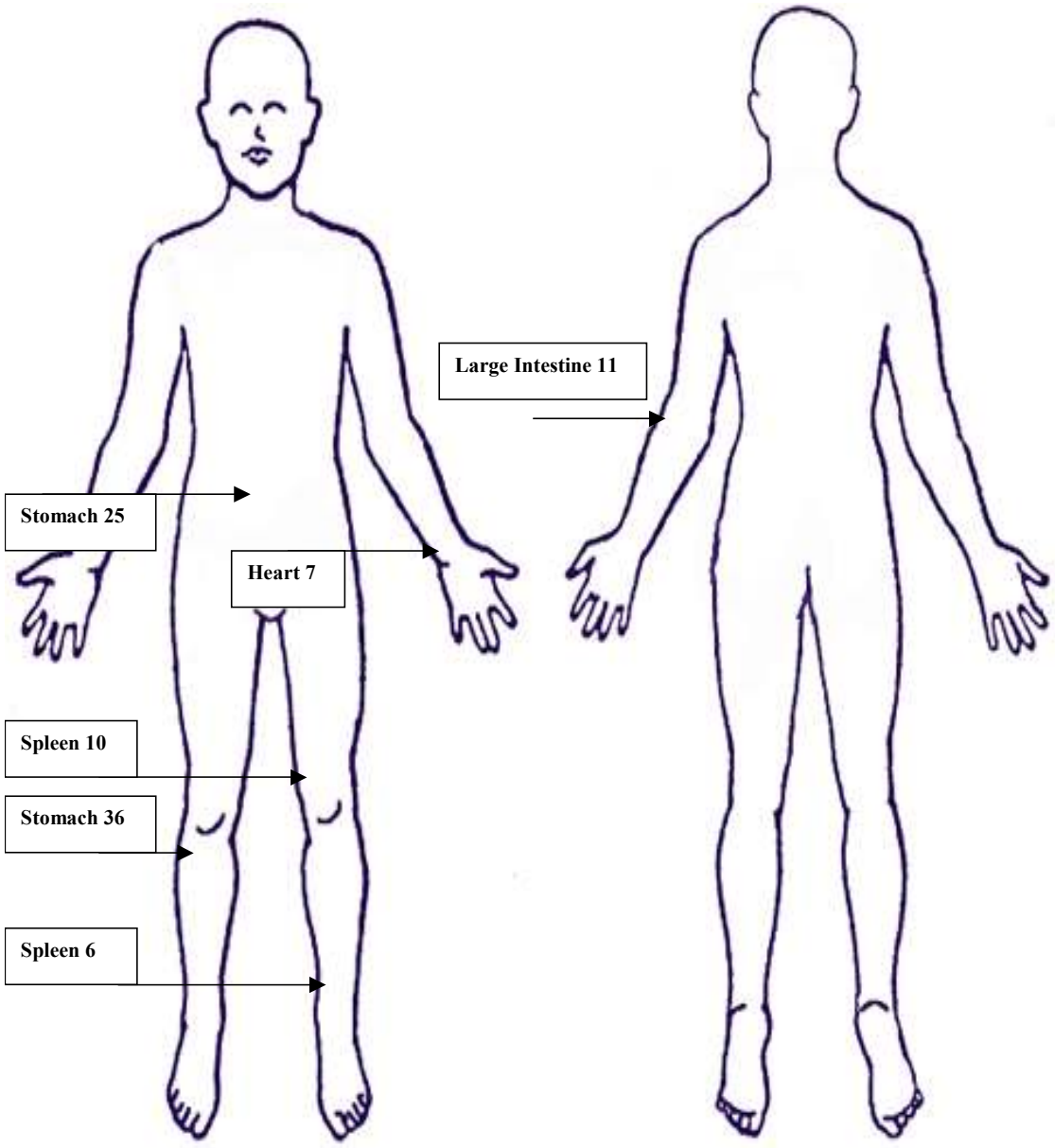

Figure 4.1: Depiction of Acu-points Common to Acupuncture Participants.

Treatment Results

Fatigue: Effects of treatment on the primary outcome, fatigue, as measured by the CFQ are shown in figures 4.2 and 4.3. Based on bimodal scoring in which scores of >3 are fatigue cases, all three of the patients were fatigue cases at baseline (Figure 4.2). The control patient remained a fatigue case until week 9, after which this participant ceased completing the CFQ. Acu1 reverted to a non-fatigue case at week 5 and remained there until week 10 when she returned to fatigue case status for 2 of the 3 remaining weeks. Acu2 remained a fatigue case at all weeks except for week 4. During most weeks the acupuncture participants were much less fatigued than the control. Patterns of response for the CFQ total scores are generally consistent with the bimodal scoring and are shown in figure 4.3. Baseline scores were 21.3 (SD 0.58).

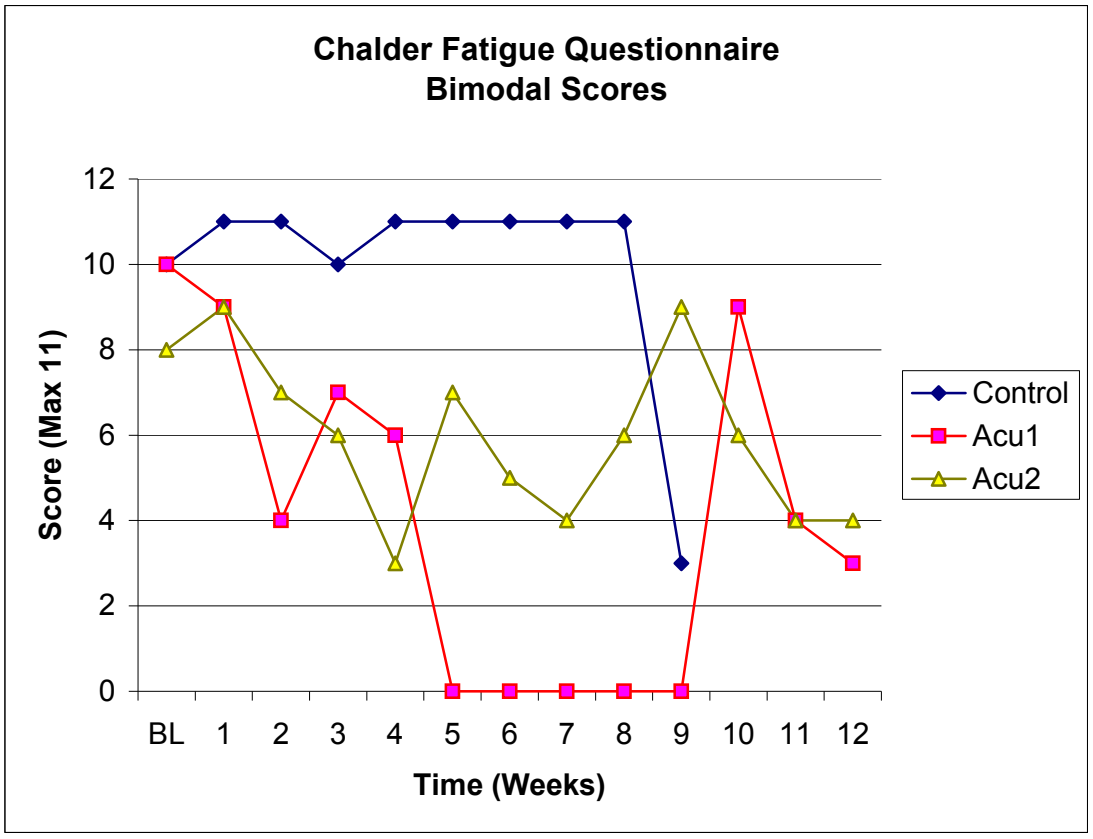

Figure 4.2: Chalder Fatigue Questionnaire Bimodal Scores

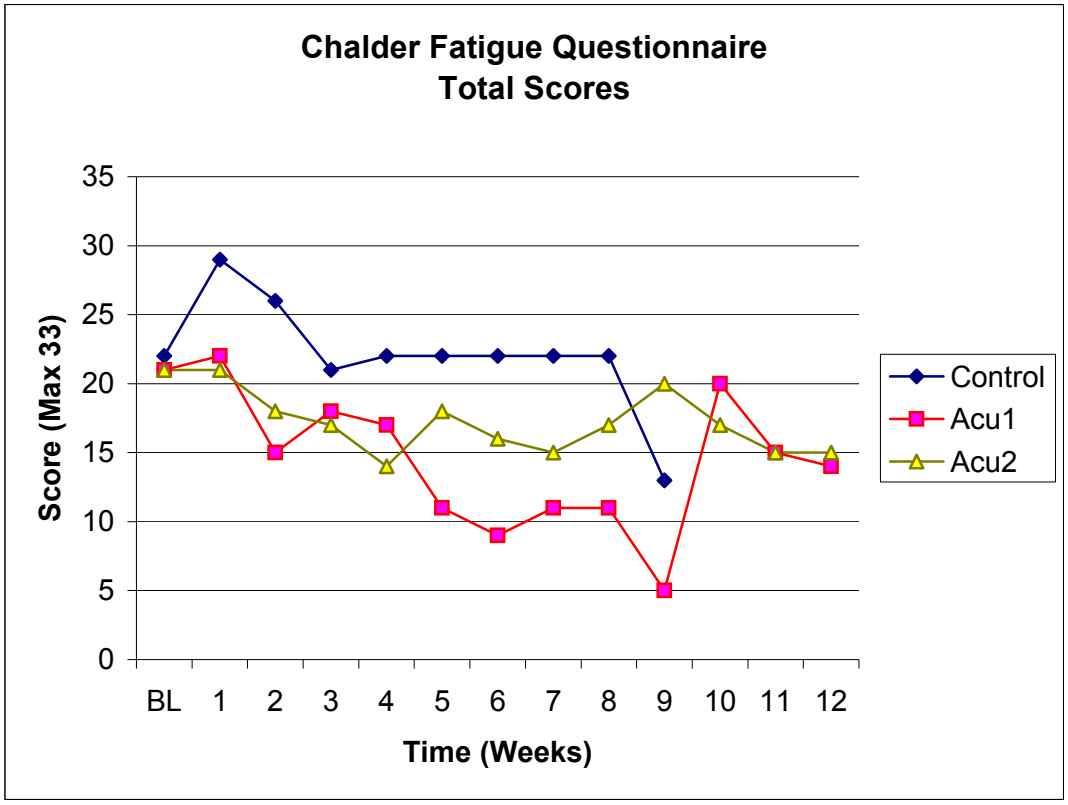

Figure 4.3: Chalder Fatigue Questionnaire – Total Scores

Quality of Life: Effects on quality of life, as measured by the SF-36, are shown in figures 4.4 - 4.12. All three participants had relatively high quality of life, as measured by the total scores, at baseline, ranging from 94 –110 (max 149), and remained relatively high throughout the study. When considering individual domains the most dramatic changes over time were seen for social functioning, bodily pain, and vitality, although this change occurred for both control and acupuncture participants. The domain in which the acupuncture patients exhibited much more change than the control was for role emotional (Figure 4.7).

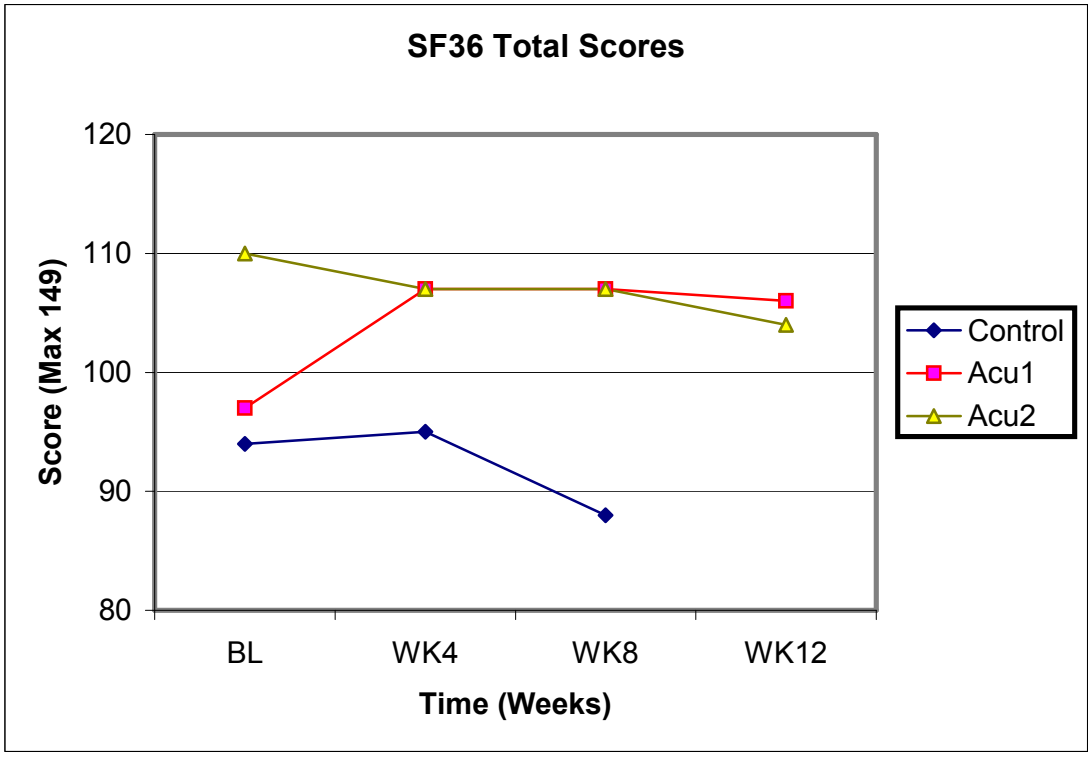

Figure 4.4: SF-36 Total Scores; maximum score = 149

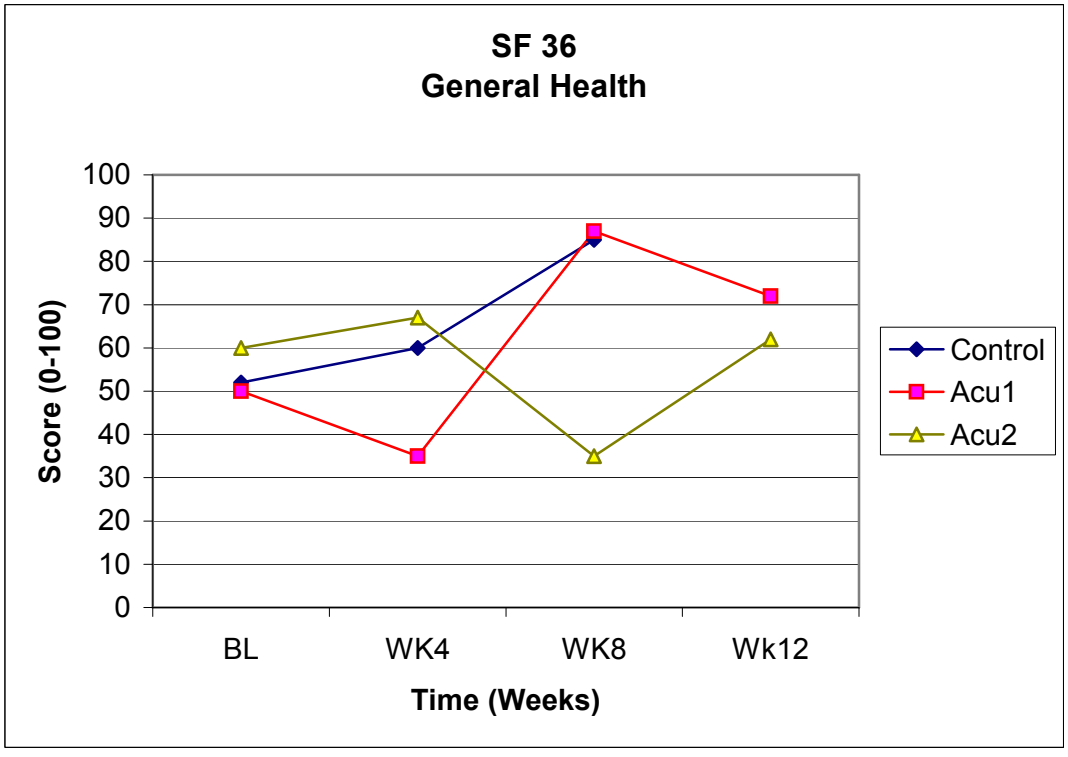

Figure 4.5: SF-36 General Health

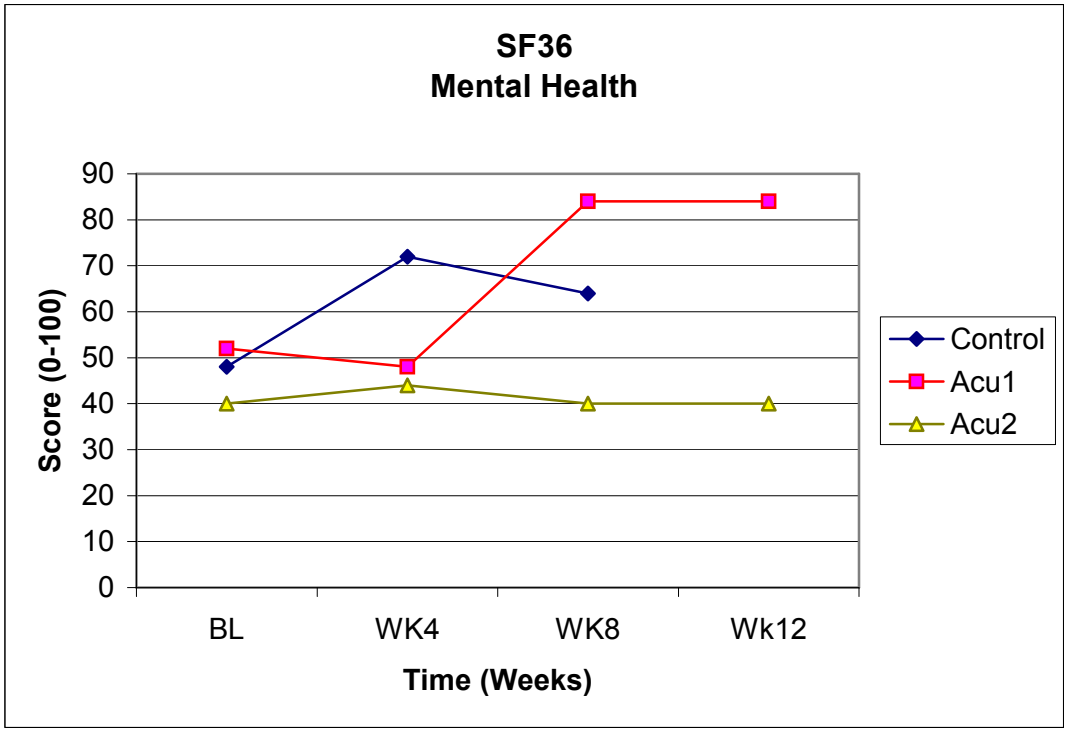

Figure 4.6: SF-36 Mental Health

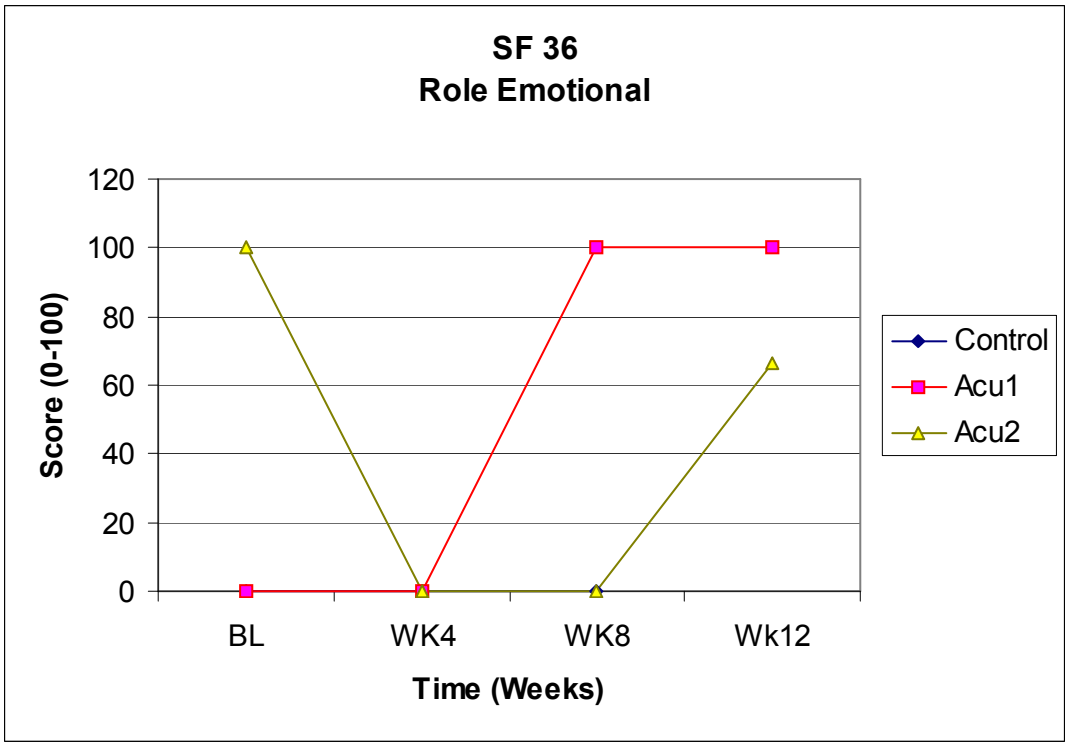

Figure 4.7: SF-36 Role Emotional

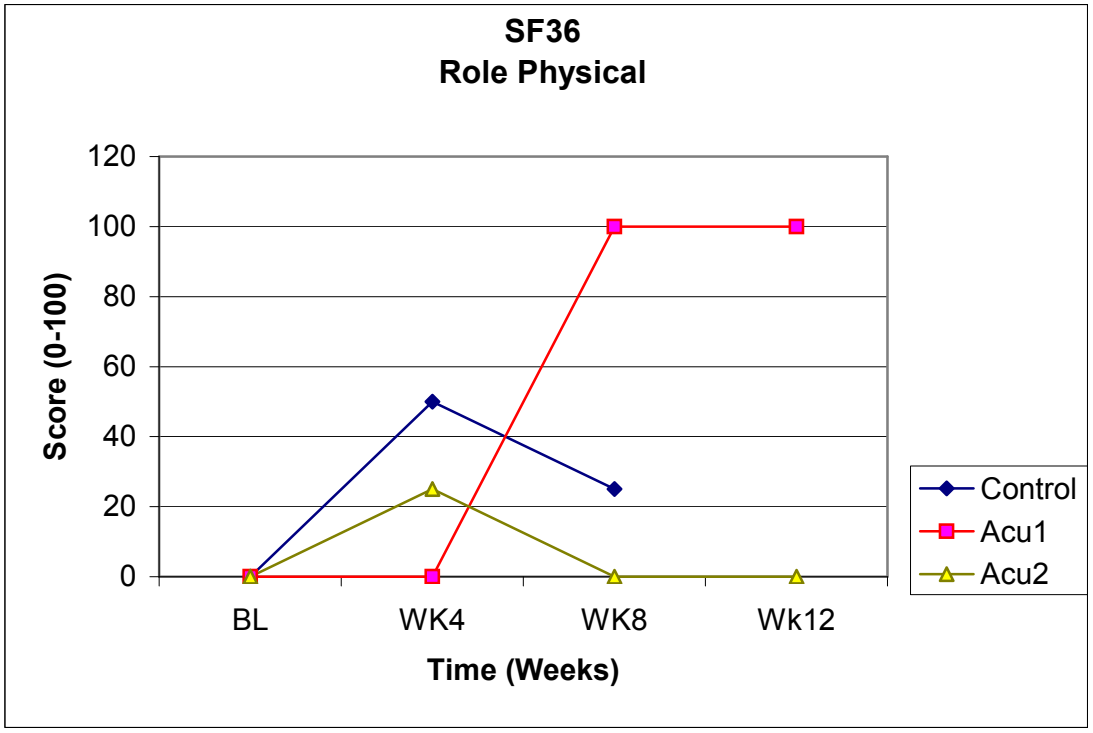

Figure 4.8: SF-36 Role Physical

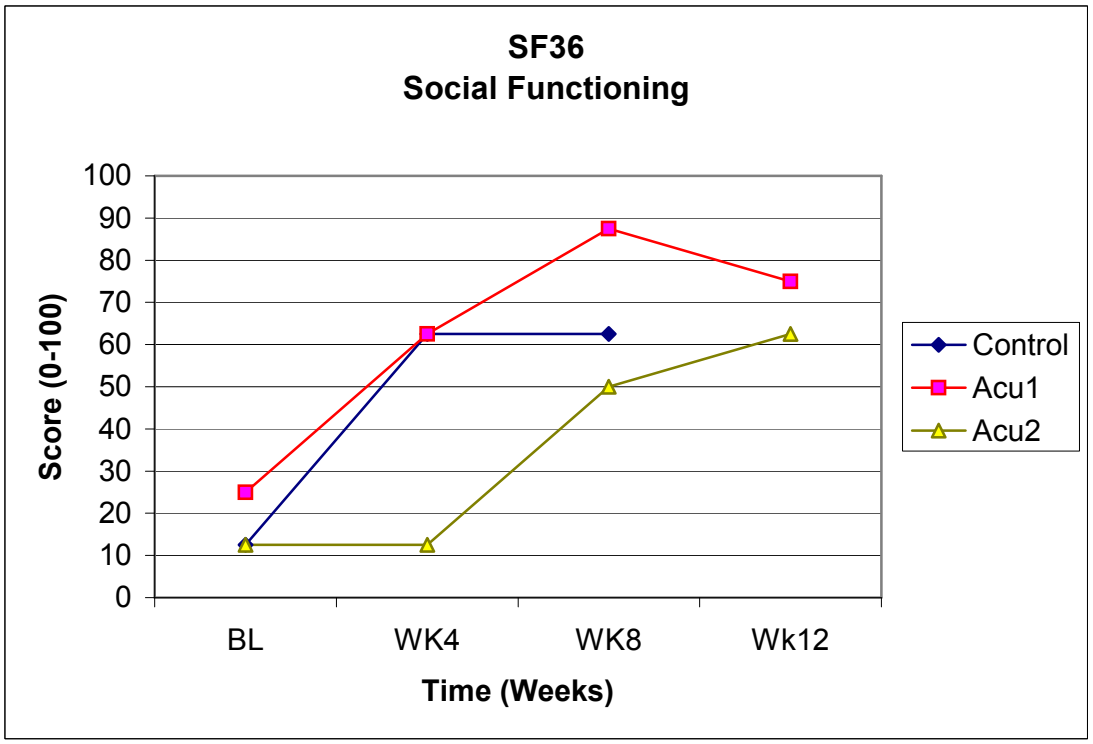

Figure 4.9: SF-36 Social Functioning

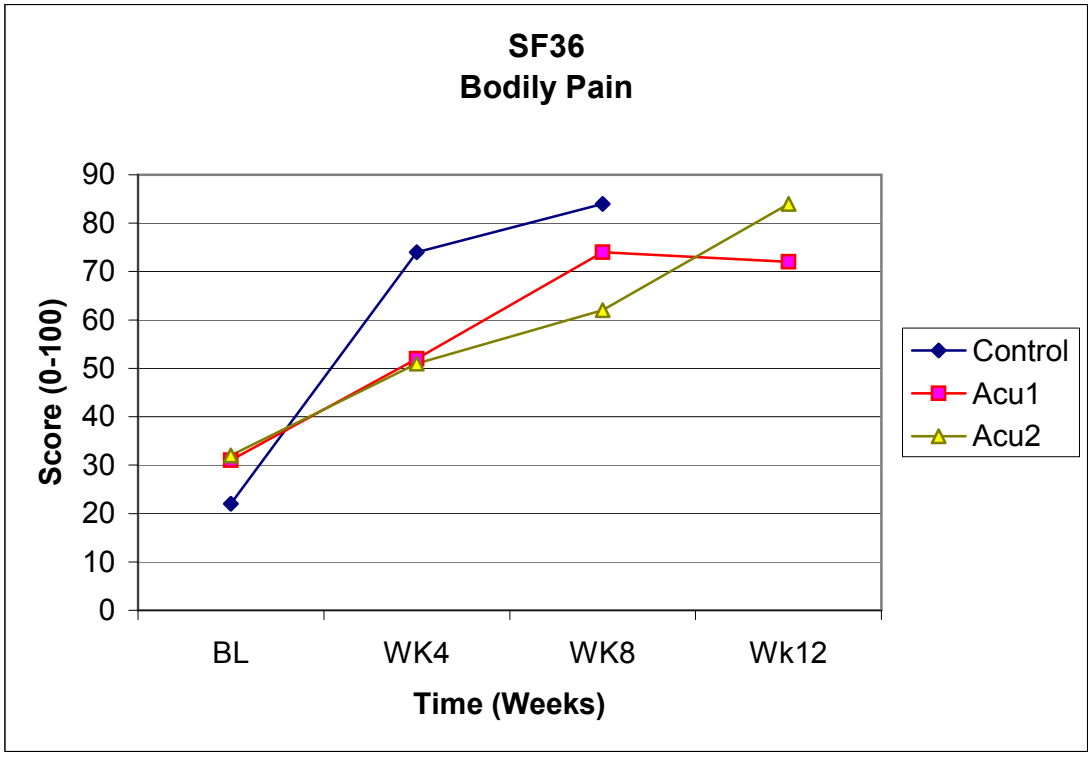

Figure 4.10: SF-36 Bodily Pain

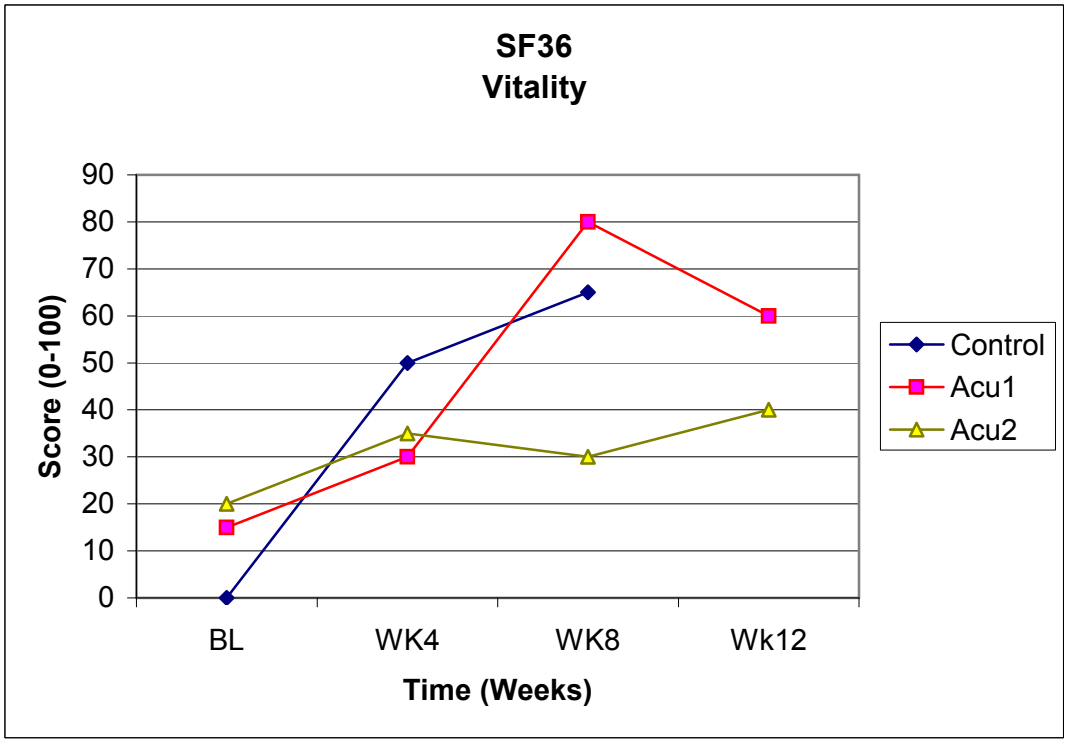

Figure 4.11: SF-36 Vitality

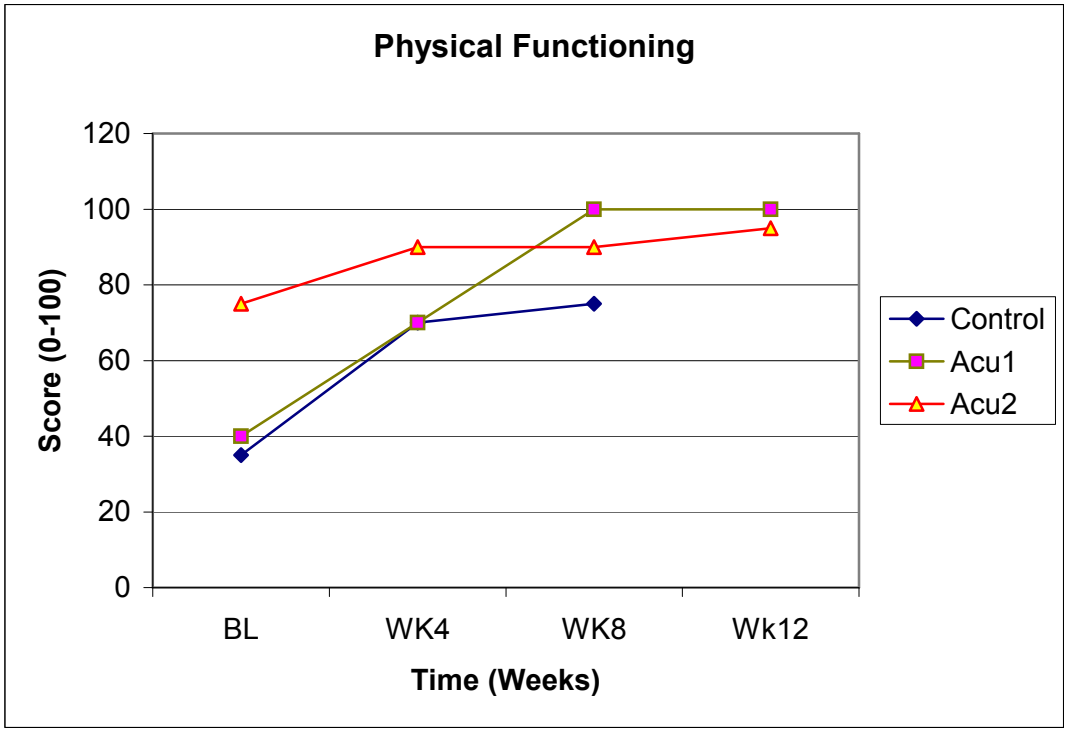

Figure 4.12: SF-36 Physical Functioning

Symptom Change: Effects on other mono symptoms are shown in figures 4.13 - 4.24. Patients were asked how much each symptom bothered them during the previous week and were scored as 1 = not at all, 2 = a little bit, 3 = moderately, 4 = quite a bit, 5 =extremely. *Sore throat*: all 3 participants were bothered moderately to extremely at baseline and resolved between weeks 4 and 7 (Figure 4.13). *Swollen glands*: all 3 participants were bothered quite a bit or extremely at baseline, which, with one transient increase at week 8 by Acu2, improved or resolved by week 5 (Figure 4.14). *Fever*: both acupuncture participants had fever at baseline, which improved by week 2 but was present at low levels throughout most of the study (Figure 4.15). *Chills*: all participants experienced chills at baseline, with resolution occurring by week 4 (Figure 4.16). *Rash:* only Acu2 had a rash at baseline, which was mild and quickly resolved with recurrence between weeks 8 and 10. The control experienced mild rash between weeks 6 and 8 only (Figure 4.17). *Cough*: all participants had a cough at baseline, to varying degrees. Acu2 and control resolved by week 2 but Acu1 had a mild or

moderate cough for most of the study (Figure 4.18). *Muscle pain*: all participants had mild or moderate pain at baseline. Acu1 had mild or no pain most weeks while the control had mild pain until week 9. Acu2 showed resolution in pain until week 6 when this symptom began to increase and peaked at an extreme level at week 8 after which it gradually decreased to a mild level at week 10 (Figure 4.19). *Joint pain*: all participants had mild or moderate joint pain at baseline, which resolved between weeks 4 and 9 (Figure 4.20). *Abdominal pain*: while Acu2 did not experience any abdominal pain, acu1 had quite a bit at baseline, which gradually improved and resolved at week 5 before recurring at week 11. The control had mild pain at baseline, which continued to week 6 when it resolved before transiently recurring at week 8 (Figure 4.21). *Loss of appetite*: both acu1 and control experienced loss of appetite quite a bit at baseline, which quickly resolved or improved to mild. Acu2 had mild symptoms at baseline, which resolved by week 1, with one recurrence at week 4 (Figure 4.22). *Nausea/upset stomach*: acu1 was similarly bothered by nausea/upset stomach quite a bit at baseline and again at weeks 3 and 4. Acu2 did not experience this symptom, while the control briefly had mild symptoms at baseline (Figure 4.23). *Vomiting*: the gastrointestinal problems of Acu1 continued with this symptom, experiencing quite a bit at baseline, which resolve by week 2. Acu2 was free of this symptom, while the control briefly had mild symptoms at baseline (Figure 4.24).

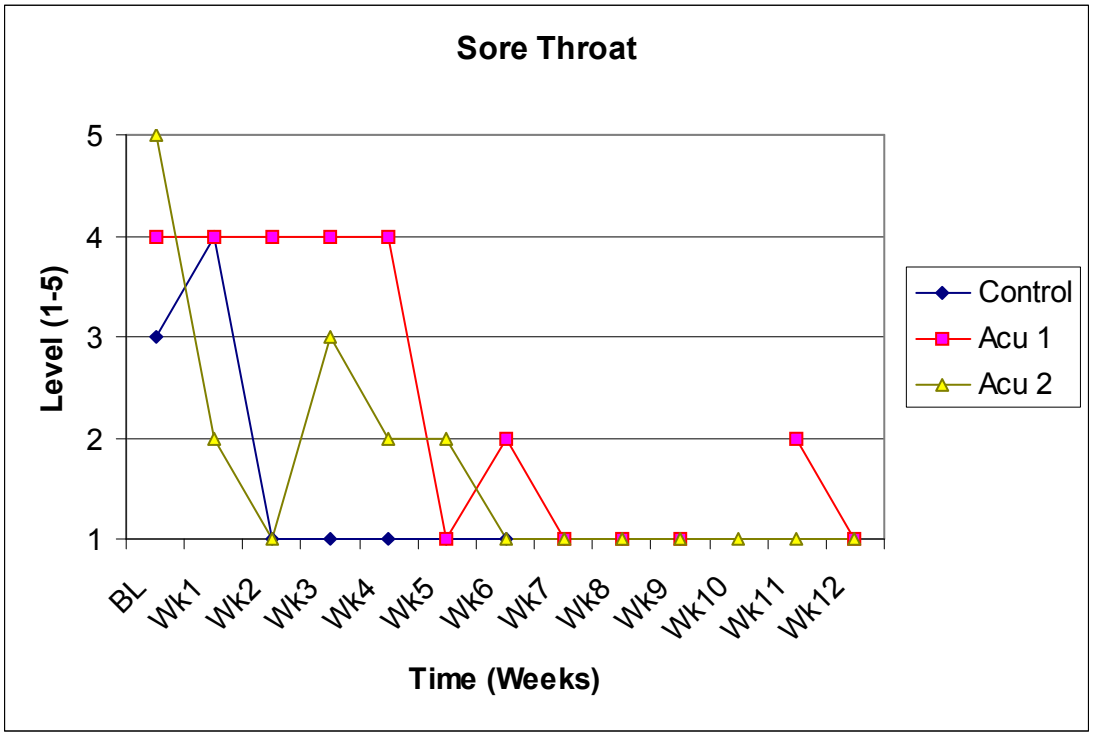

Figure 4.13: Sore Throat

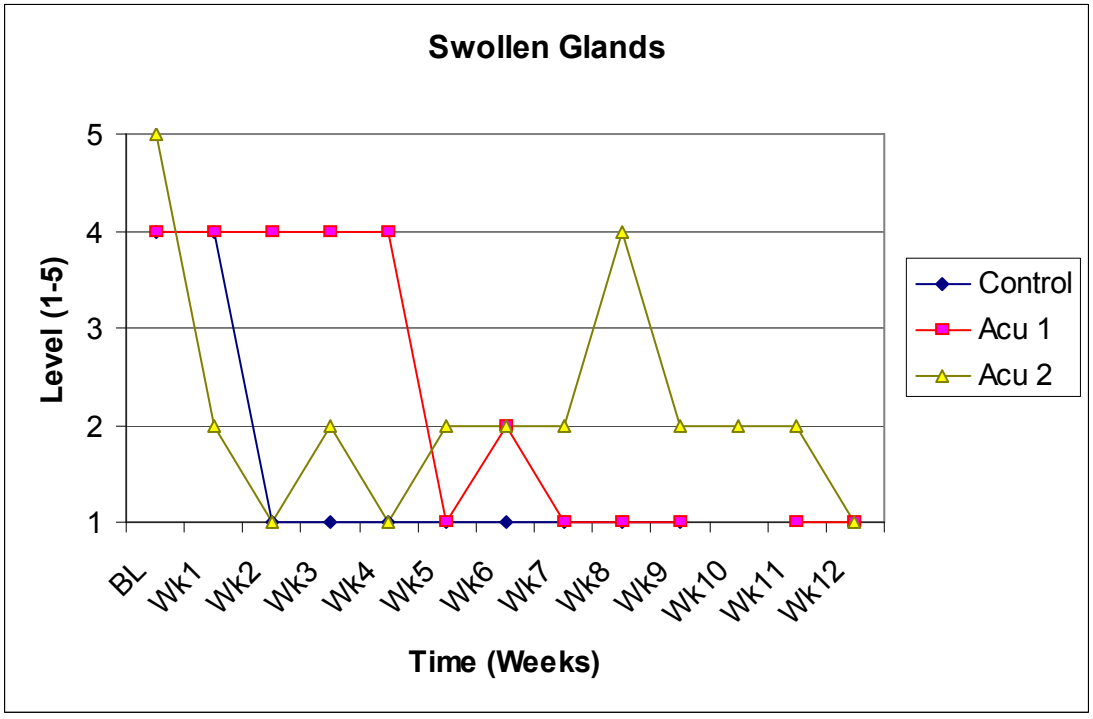

Figure 4.14: Swollen Glands

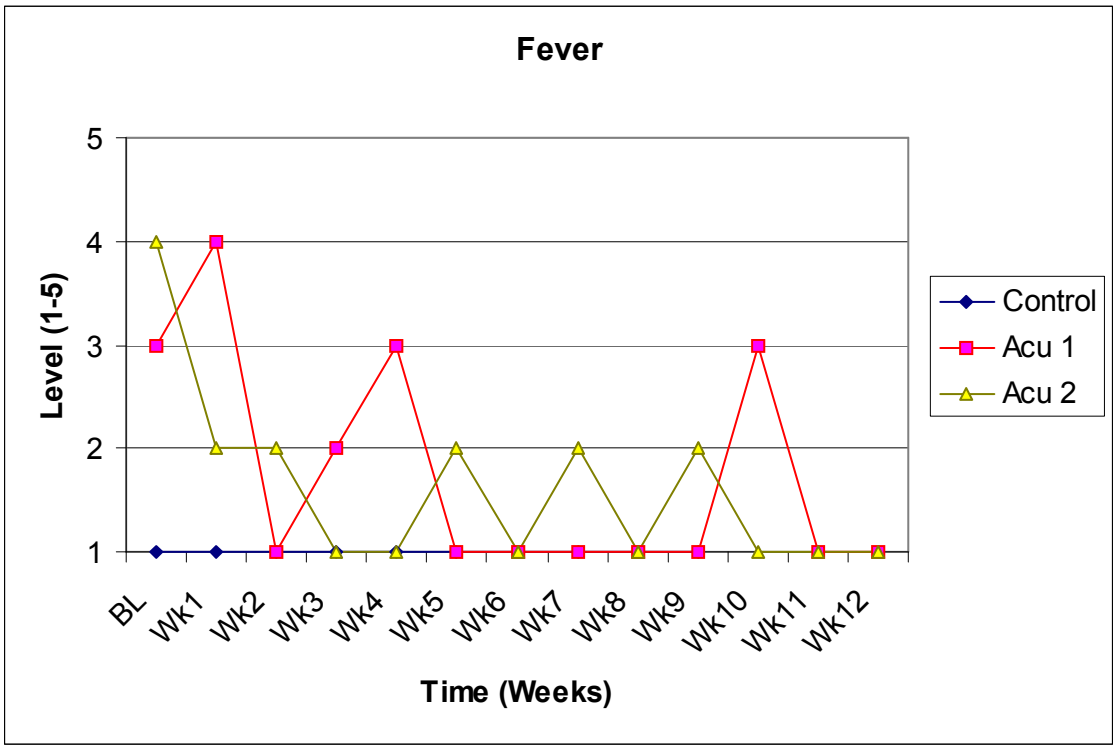

Figure 4.15: Fever

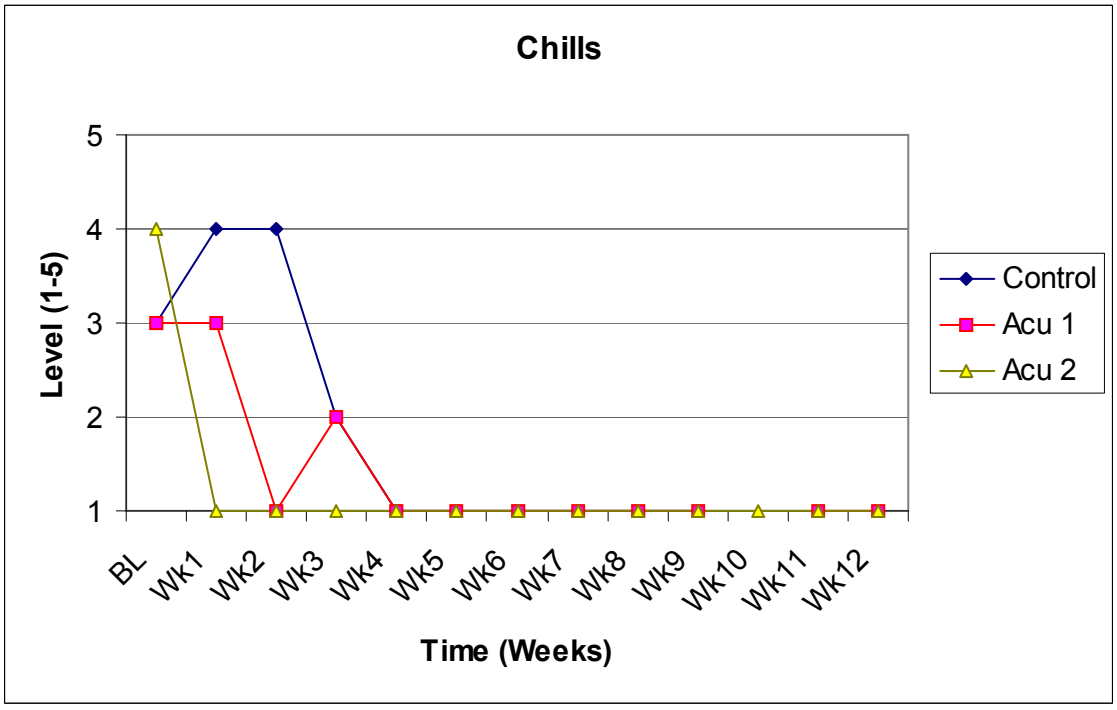

Figure 4.16: Chills

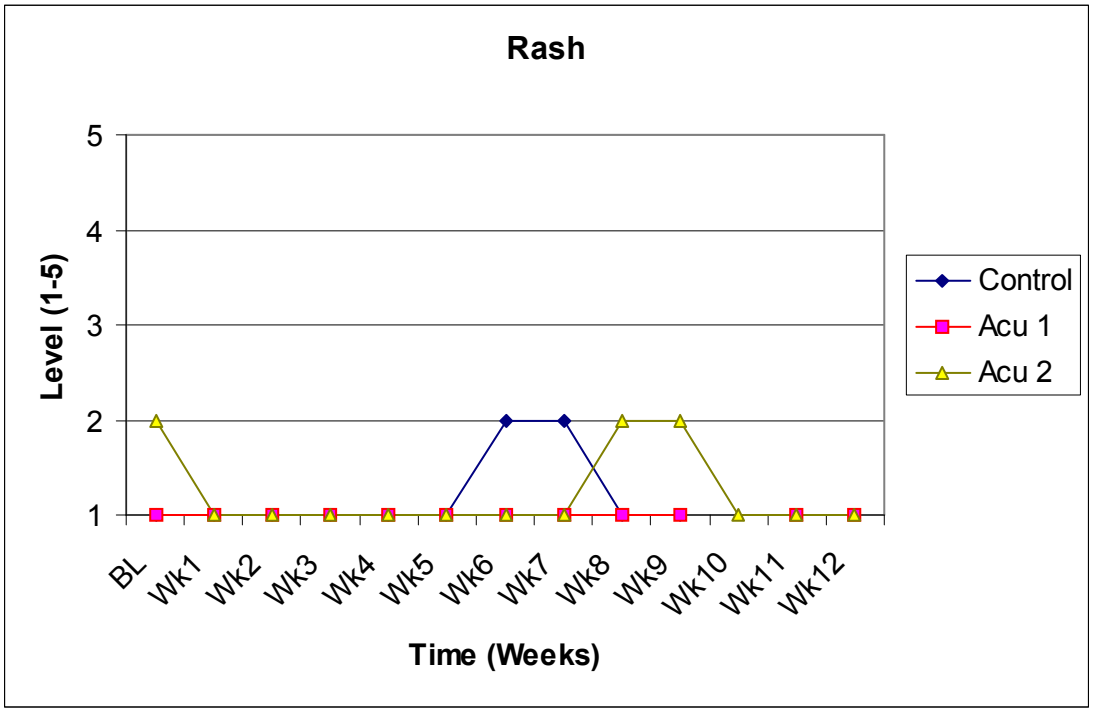

Figure 4.17: Rash

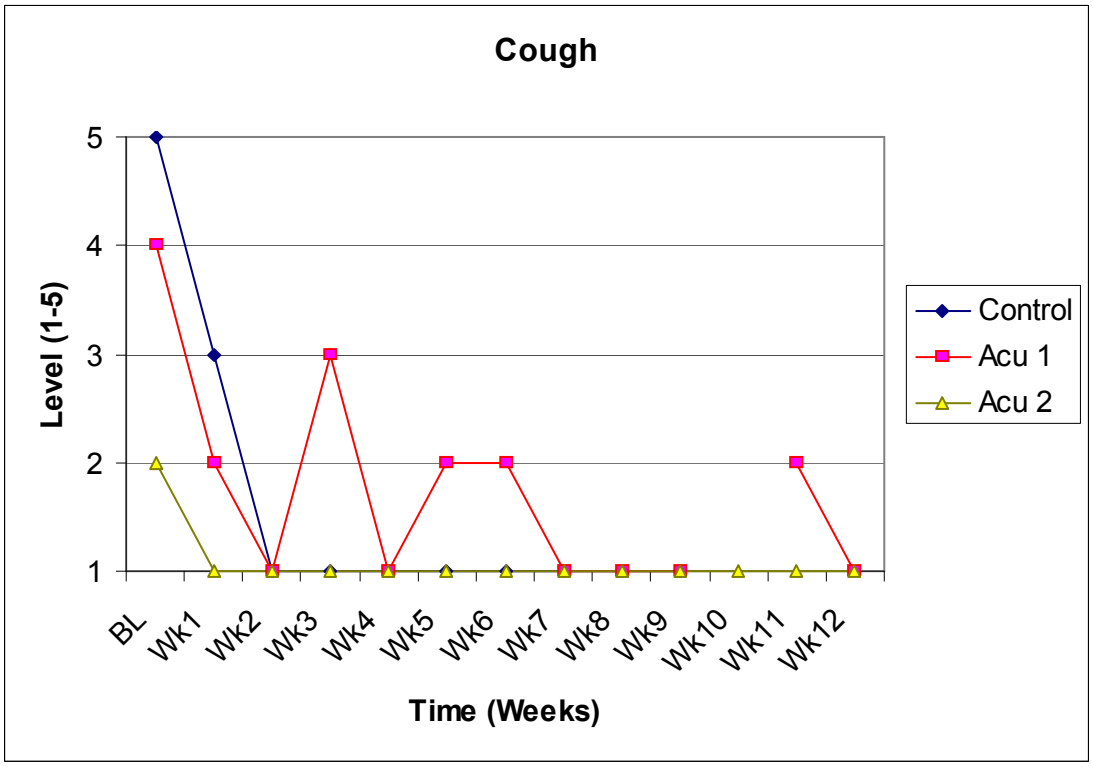

Figure 4.18: Cough

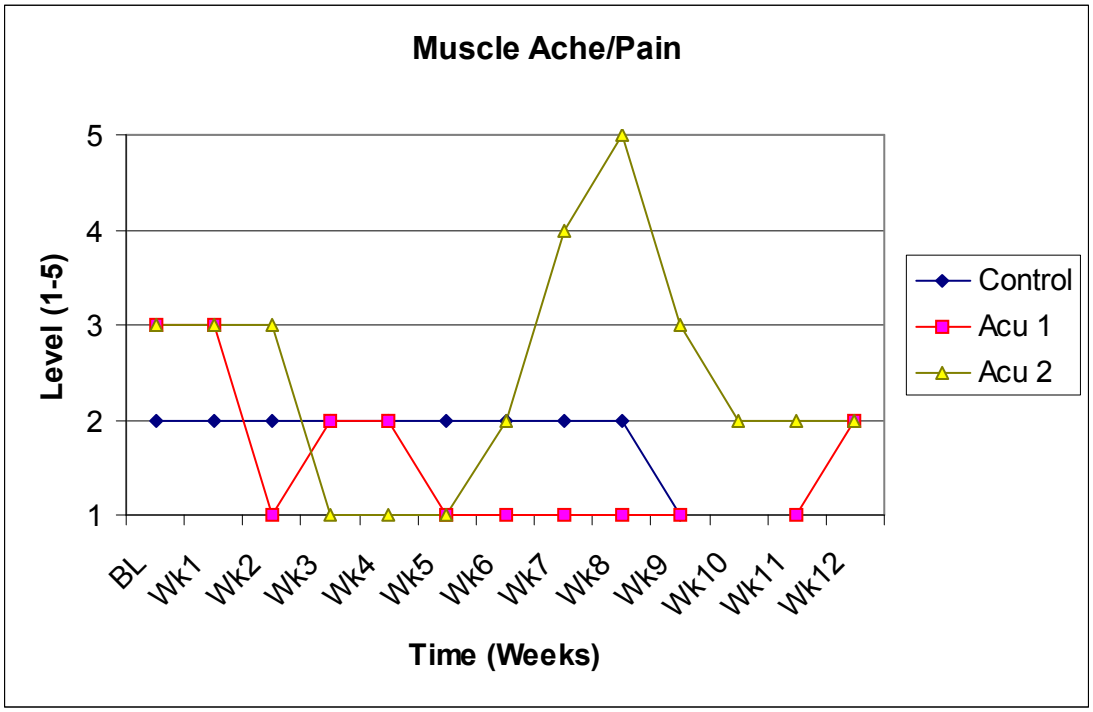

Figure 4.19: Muscle Ache and Pain

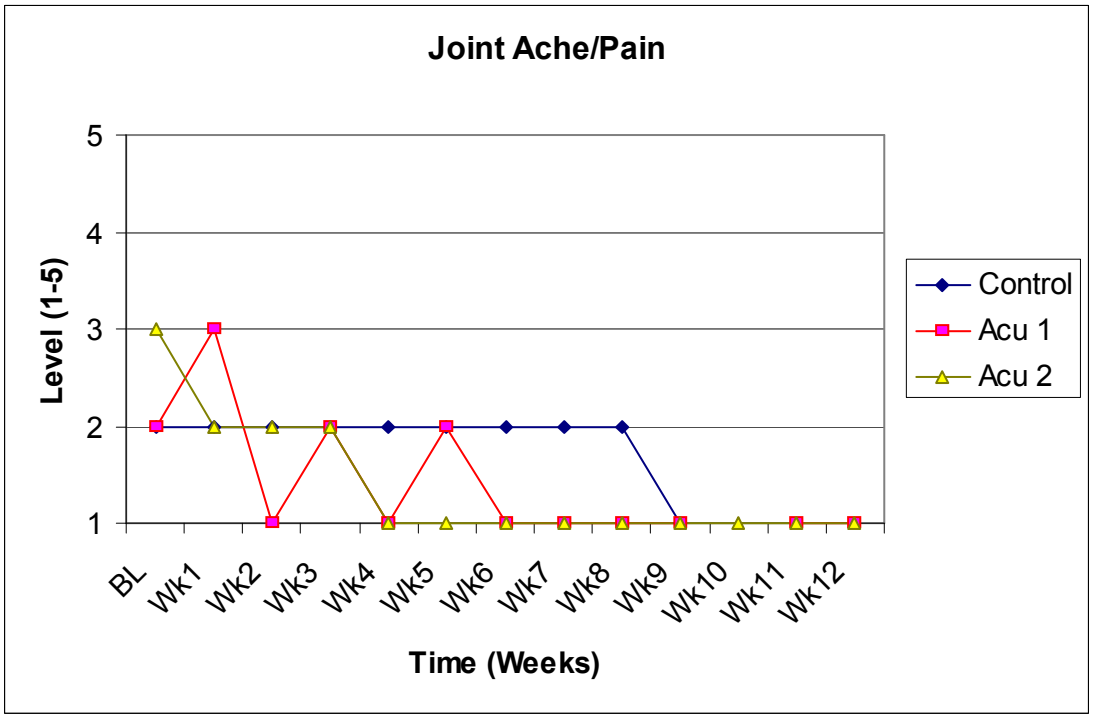

Figure 4.20: Joint Ache and Pain

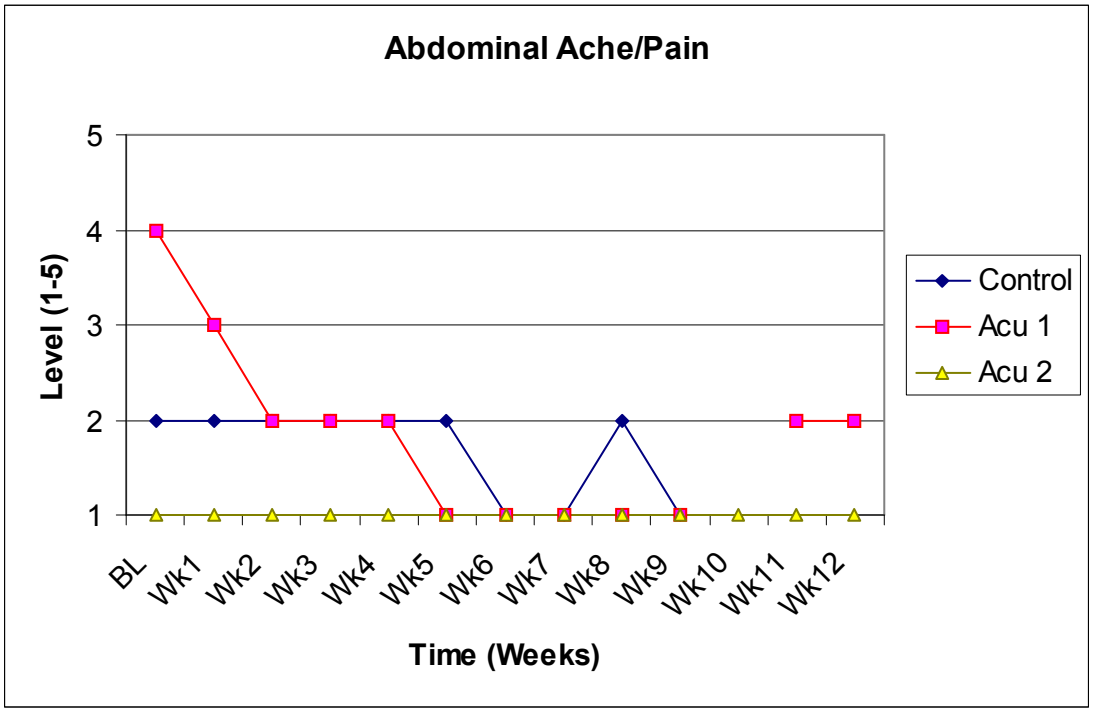

Figure 4.21: Abdominal Ache and Pain

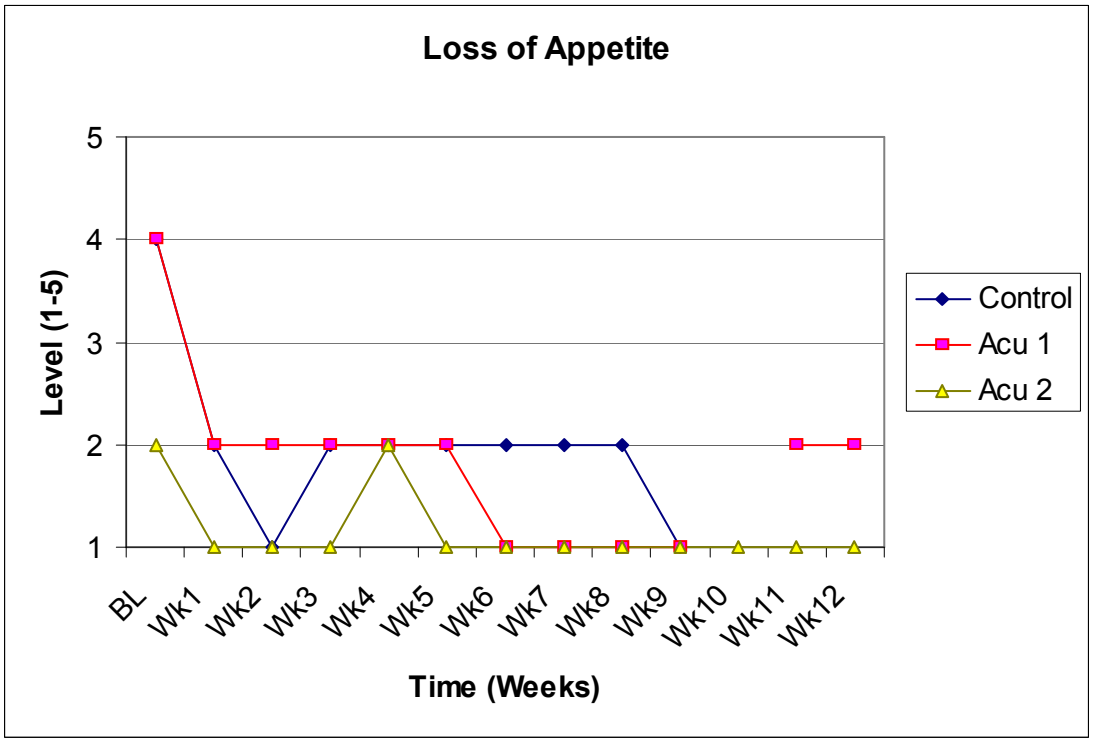

Figure 4.22: Loss of Appetite

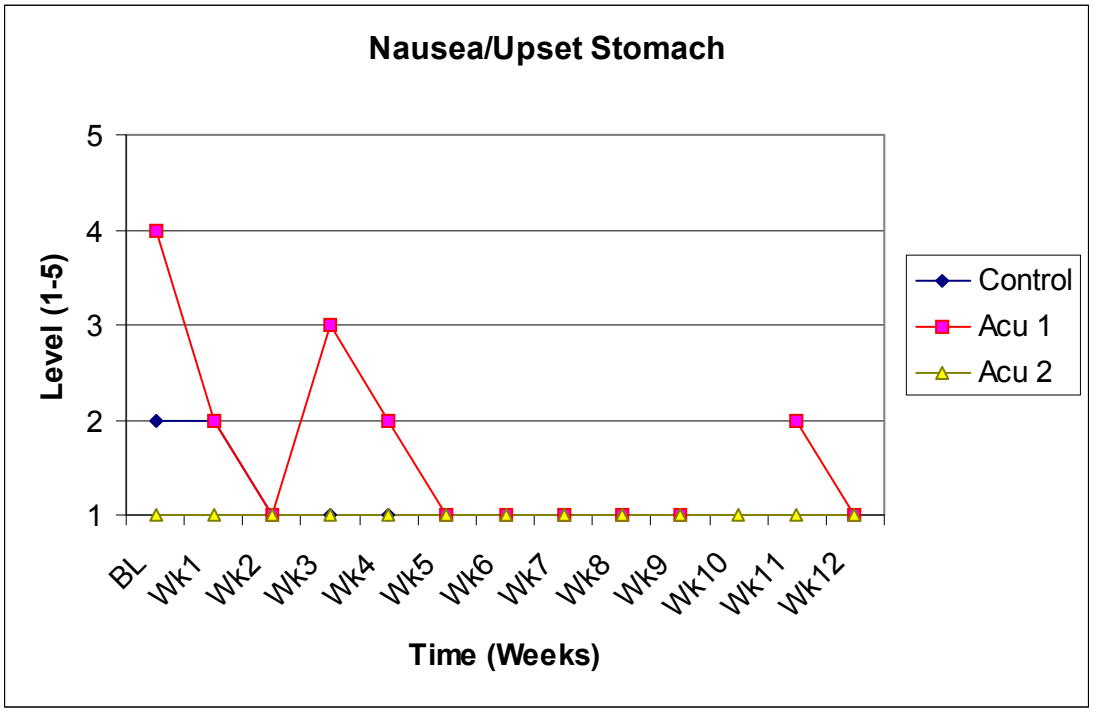

Figure 4.23: Nausea and Upset Stomach

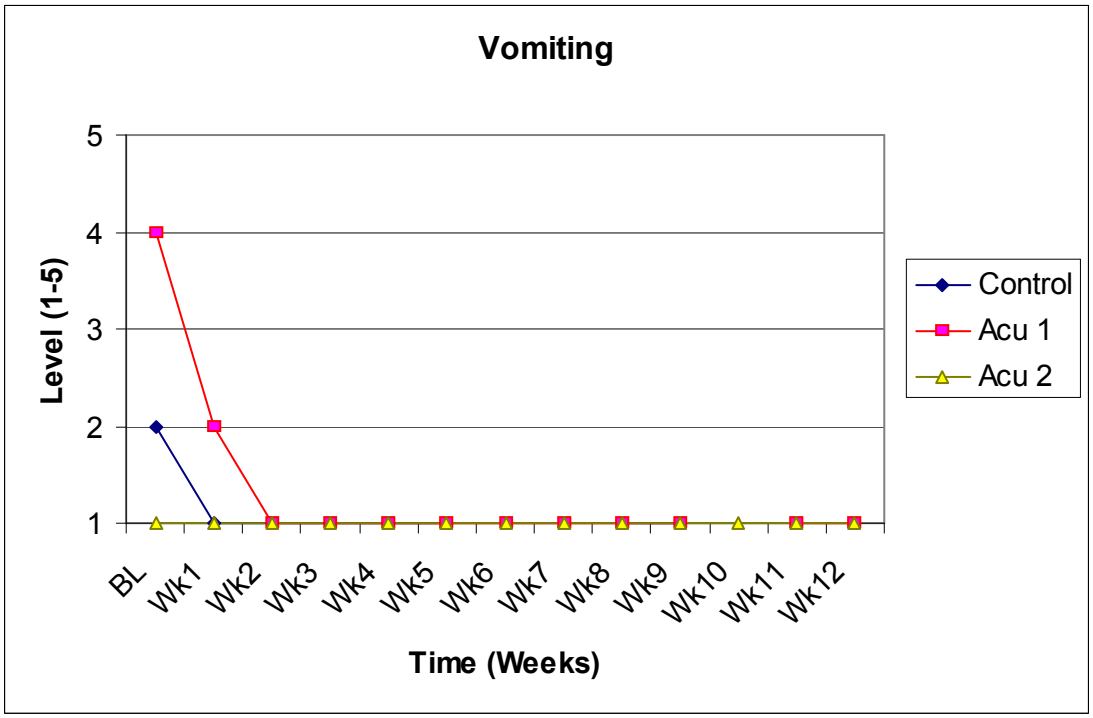

Figure 4.24: Vomiting

Absence from School or Work: Other than one absence during week 1 by the control there were no absences from school or work reported.

Medication Use: All three participants used an analgesic during the first week; this use continued for Acu1 through to week 6. Acu2 also used an antibiotic during week 1 for suspected but unverified strep throat. She then used vitamin C from weeks 3 to 5 and a hot wheat sack for a sore neck between weeks 8 and 12.

Acupuncture Effects: Effects noted during the treatment period, including both positive and negative effects, experienced at least once, are listed in table 4.6. All of the negative effects were transient and mild; none required medical attention.

Table 4.6: Acupuncture Effects Noted During Treatment Period

Effect	Acu1	Acu2
Feel relaxed	+*	+*
Feel energized	+*	+*
Tiredness or drowsiness	+*	+*
Pain/discomfort at needle site	+	+
Pain/discomfort at other site	+	
Bruising	+	+
Feeling faint or dizzy	+	
Bleeding at needle site	+	+
Insomnia/not being able to sleep	+*	
Itching/irritation at needle site	+	
Aggravation of existing condition (knee pain)	+	

Acu1 = first acupuncture participant; Acu2 = second acupuncture participant
*indicates levels 3 (quite a bit) or 4 (extremely) reported, otherwise levels 1 (a little bit) or 2 (moderately) reported

4.4.2 Infectious Mononucleosis Population Characteristics

Capital Health Region (CHR) data on Monospot tests were obtained and analyzed for the period between April 2003 and July 2008. Since the database from which this information was obtained was initiated April 1, 2003, data for the first three months of 2003 were missing and so the annual incidence for 2003 was estimated based on the data for the remaining nine months. The requested data did not include place of residence so we cannot preclude some of the positive Monospot cases from residing in health regions other than Capital Health. If we assume all cases resided in the CHR, we may be overestimating the local incidence rate. Under this assumption, the annual rate of positive Monospot tests for the period April 2003-July 2008 is 1.11 per 1000 people per year (95% CI (0.95–3.2)). If we assume that a certain number of the positive cases resided in other regions, the rate decreases accordingly: for example, if 5%, 10%, and 20% of the positive cases came from individuals residing elsewhere, the corresponding overall incidence rates are 1.06/1000, 1.00/1000, and 0.89/1000 per year, respectively. There was a relatively even split between male and female cases with no statistically significant difference in the proportion of females between years (p=0.160) (Table 4.7).

Table 4.7: Capital Health Region (CHR) Monospot Positive Incidence Rates for 2003- 2007

Year	Monospot Positive Cases	Age Range	Female N (%)	Population* All Ages	Incidence Rate: All ages (per 1000 people)
2003	1049**	4-86	413 (52.5%)	981 715	1.07**
2004	1174	4-85	653 (55.6%)	993 921	1.18
2005	1161	2-87	652 (56.2%)	1 005 348	1.15
2006	986	3-85	510 (51.7%)	1 027 553	0.96
2007	1290	2-73	708 (54.9%)	1 064 652	1.21
Mean (SD)	1132.0 (111.81)**	2-87	54.4%	1 014 100	1.11 (0.100)**

* mid-year values from Government of Alberta Health and Wellness Interactive Health Data Application; www.ahw.gov.ab.ca/IHDA_Retrieval/selectSubCategoryParameters.do#; (accessed Sept 23 2009); **9 months April-Dec 2003; calculated based on annual 2003 estimate calculated from 9 months value of 787 cases

The age group 15-25 made up approximately 80% of all cases. The proportion made up by this age group did not differ significantly between years (p=0.067). The overall incidence rate in this population was 5.46 per 1000 people per year (95% CI (0.89–10.0)) (Table 4.8). Considering again the possibility of residence of cases in other health regions, for 5%, 10%, and 20% external residence, the rate decreases to 4.87/1000, 4.61/1000, and 4.10/1000 per year, respectively.

Table 4.8: Capital Health Region (CHR) Monospot Positive Incidence Rates for 2003-2007 for 15-25 Year Old Group

Year	Monospot Positive Cases 15-25 years N (% of total cases)	Population* 15-25 years	Incidence Rate: 15-25 group (per 1000 People)
2003	848** (80.8%)	159 004	5.33**
2004	953 (81.2%)	161 909	5.89
2005	931 (80.2%)	163 416	5.70
2006	754 (76.5%)	167 106	4.51
2007	1012 (78.4%)	172 960	5.85
Mean (SD)	899.6 (100.4)**	175 466	5.46 (0.573)**

*mid-year values from Government of Alberta Health and Wellness Interactive Health Data Application; www.ahw.gov.ab.ca/IHDA_Retrieval/selectSubCategoryParameters.do#; (accessed Sept 23 2009); **based on 9 month case number of 636

In order to determine how closely our population conformed to the published data on mono, we investigated the relationship between Monospot positive cases, age, and time. Plotting the number of cases by age gave the age distribution (Figure 4.25). The number of cases was consistently low for those under the age of 15 and over the age of 30, peaking between ages 16 and 21.

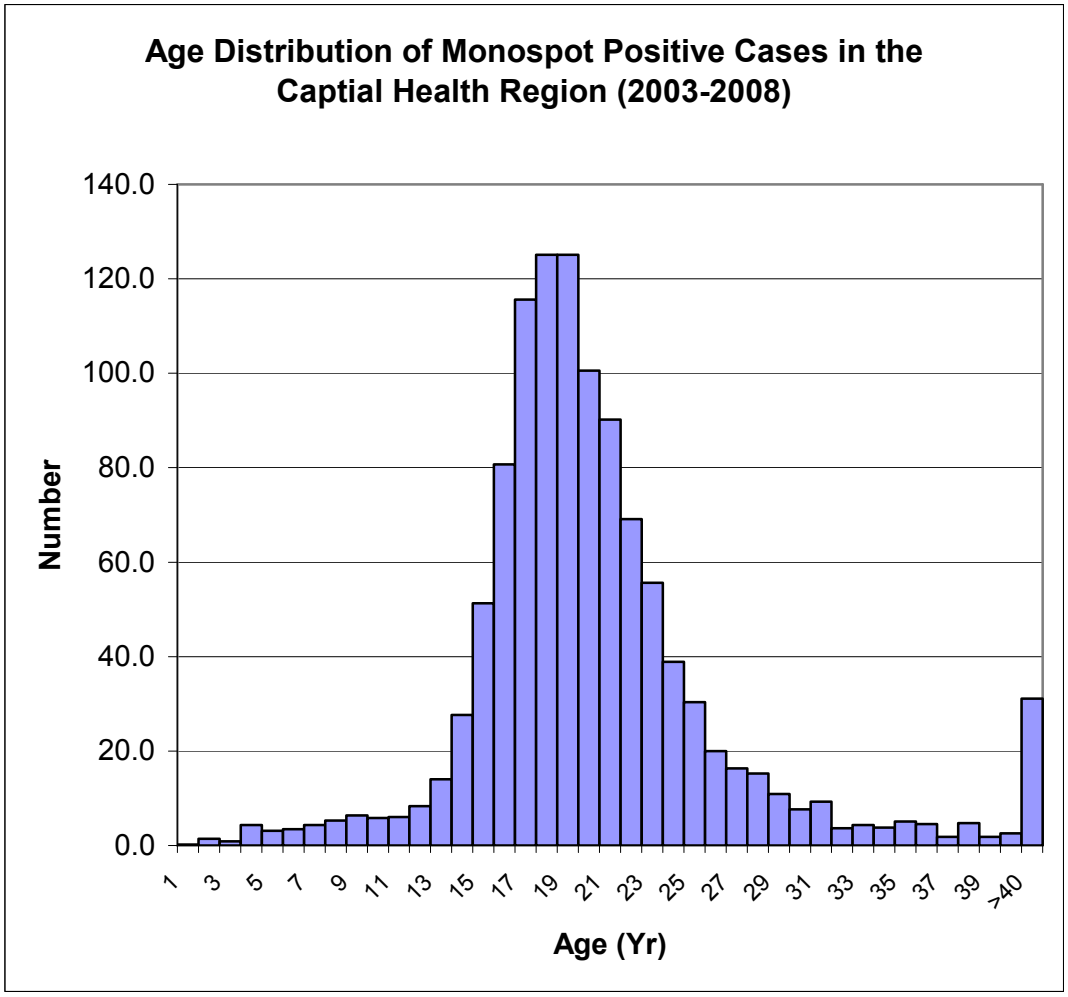

Figure 4.25: Age Distribution of Monospot Positive Cases Between April 2003 and July 2008

Likewise, plotting the number of cases per month over time gave a temporal distribution (Figure 4.26). Examination of the graph does not show clear patterns over time, either in change between months or between years. For example, a distinct seasonal pattern is not apparent. Striking variations in the counts are apparent for April 2008, where the counts are much higher, and for October 2006, where the counts are much lower than for surrounding time points. In order to check if our patient population (15-25 years) had a different temporal distribution than the overall group we repeated these analyses for this age group alone (Figure 4.27). Similar patterns were observed as compared to the overall group.

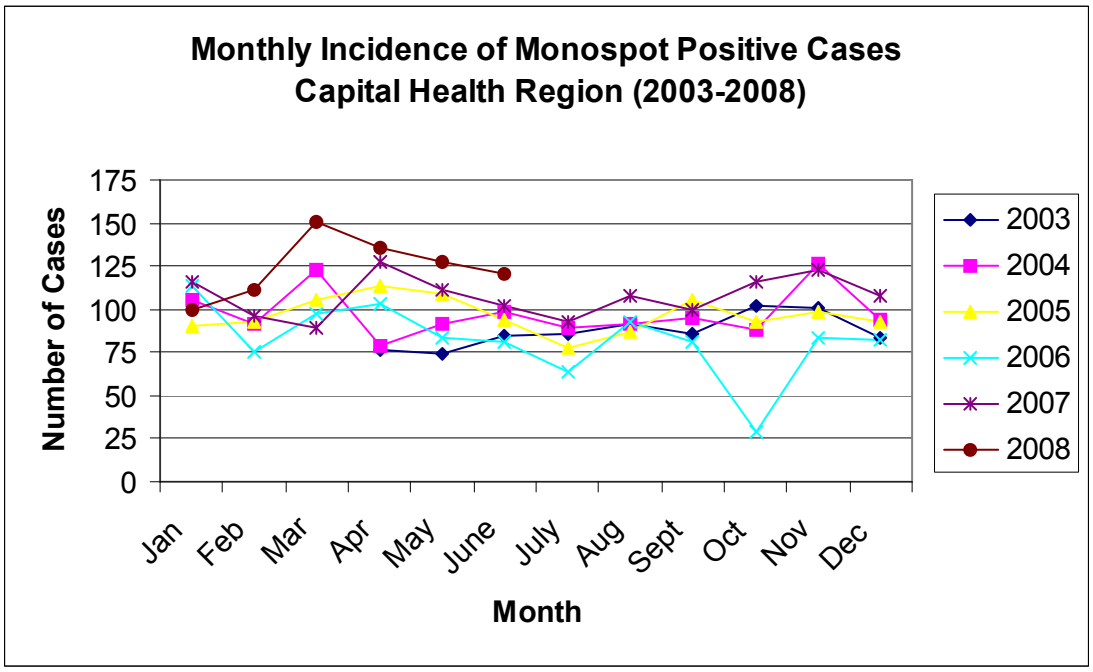

Figure 4.26 Temporal Distribution of Monospot Positive Cases Over 12 Months - All Ages

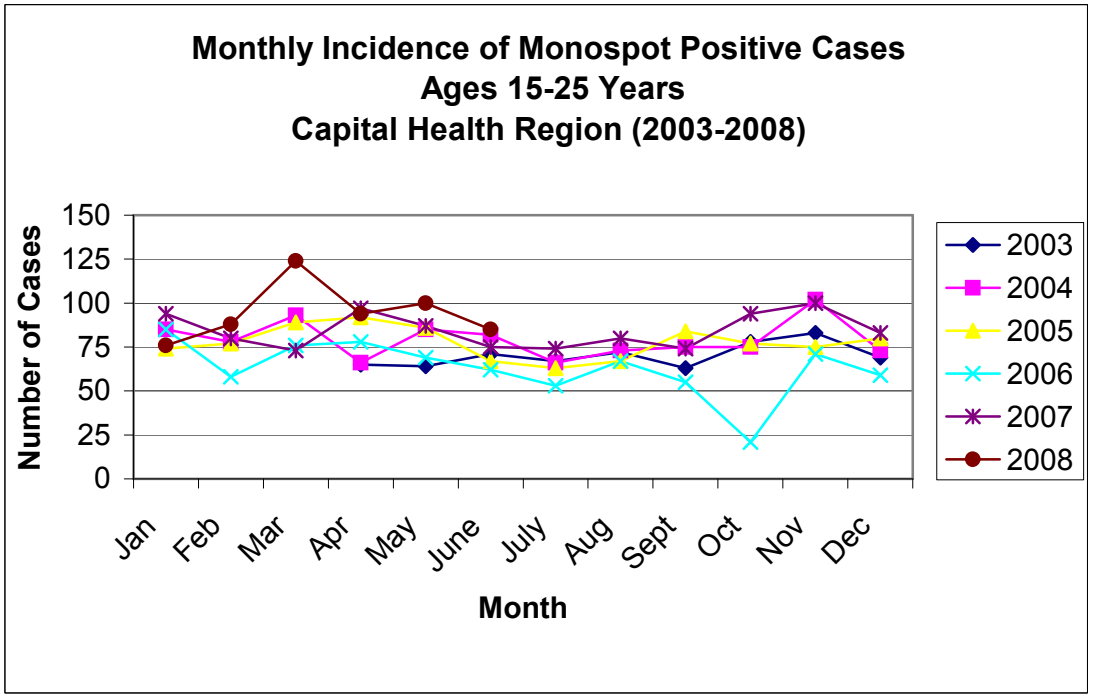

Figure 4.27 Temporal Distribution of Monospot Positive Cases Over 12 Months - 15-25 Year Old Group

Two Poisson regression analyses were performed, one for all ages combined and one for the 15-25 year old group alone. Month and year variables were included together in the models; a likelihood ratio test demonstrated that inclusion of these variables was appropriate ($p<0.001$).

All ages data

With respect to variation over years, compared to 2005, we see a small but statistically significant decrease in rate for year 2006 (rate ratio (RR) = 0.83; 95% CI (0.76–0.90); $p<0.0001$), and a small, significant increase for 2008 (RR = 1.16; 95% CI (1.05–1.27); $p=0.0030$).

With respect to variation over months, compared to April, we see differences, but few that are statistically significant (Feb RR = 0.86; 95% CI (0.76–0.97); $p=0.0145$, July RR = 0.81; 95% CI (0.71-0.92); $p=0.0009$, Oct RR = 0.84; 95% CI (0.75–0.96); $p=0.0074$).

15-25 year data

With respect to variation over years, compared to 2005, we again see a small, statistically significant decrease in rate for 2006 (RR = 0.79 (95% CI (0.71–0.87); $p<0.0001$) but the statistical significance for 2008 (RR = 1.09; 95% CI (0.98–1.22); $p=0.1000$) has been lost.

With respect to variation over months, compared to April, we see differences, but only one that is statistically significant (July RR = 0.82; 95% CI (0.71–0.94); $p=0.0049$ and one that approaches statistical significance (Oct RR = 0.87; 95% CI (0.76–1.00); $p=0.052$), and fewer than for the all age group.

4.5 Discussion

To our knowledge this was the first RCT of acupuncture for infectious mononucleosis.

Recruitment Issues

The most significant limitation to our study was patient recruitment, which involved the following four approaches: institutions/medical centres, individual physicians, patients, and diagnostic lab. Some of these approaches were used successfully in previous mono studies, such as in Candy et al., who had physicians in five clinics and a student health centre notify patients of their study and obtain consent for follow up contact by study personnel (Candy 2004). Access to diagnostic lab results was used by Katon et al., where medical personnel at the lab contacted eligible patients directly (Katon 1999).

Institutional Level

It was hoped that one or both of the two types of walk-in health centres, the MediCentres and the University Student Health Centre, would participate, at the institution level, in recruitment. Based on incidence data, the MediCentres and Student Health Centre were expected to see 206 and 44 Monospot positive cases, respectively, during our recruitment period. With our 18% enrolment rate, this may have provided 45 enrolled participants.

The local MediCentre administration was asked to aid in notification of their physicians of this study and for assistance in encouraging participation. Unfortunately this request was denied on the grounds of potential liability issues. The University Student Health Centre was likewise approached and responded that their institution does not participate in research. In both cases we were allowed to approach physicians in these centres and ask for individual participation.

Individual Physician Level

Physicians at each of these two centres, as well as at other area clinics, were invited to participate. The most common reason given for not participating was 'seeing few mono cases' in their individual practices, which reinforced the reasoning behind our attempt to involve the busy centres, at the institutional level. The second most common reason was 'being too busy' for research. Despite this we were able to recruit nine physicians in private practice and six who practiced out of the walk-in clinics, one at each of six sites. These physicians agreed to notify not only the mono cases they personally saw but those of their colleagues in the same clinic, if possible, however, it is unlikely that these physicians were able to monitor and contact all mono cases within their clinics.

Patient Level

Once it became clear that our participant recruitment through physicians was having limited success, we attempted to contact patients directly. Methods used included posting ads in busy walk-in clinics, including those already approached, as well as in post-secondary student newspapers and list-serves. These methods generated some queries about the study but no eligible participants, however, these methods were not employed until late in the recruitment period.

Diagnostic Lab Level

A fourth potential point of patient access was the large diagnostic lab that performed most of the Monospot tests for the region. We asked if they would participate in one of two ways, either through direct notification of this study to Monospot positive patients or to referring physicians at the time the test results were returned. Both requests were denied.

Health Research Ethics Board Level

In preparation for our trial, patient recruitment strategies were discussed with our local Health Research Ethics Board (HREB) along with the difficulties and barriers to accessing our mono population, however, HREB personnel maintained that patient contact strategies must comply with local health information legislation that limits patient contact to their own physician or an approved custodian of their health information.

Two key publications that discuss privacy issues related to medical research in Canada are the Alberta Health and Wellness (AHW) Health Information Act (AHW 1999) and the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (CIHR 1998). These documents are part of international initiatives to change ethical norms and protect human rights in scientific and medical research that date back to the Nuremberg Code and the Helsinki Declaration.

Access to patient information in the province of Alberta is severely restricted by local legislation (AHW 1999). The AHW Health Information Act (HIA), published in 1999, was intended to establish strong and effective mechanisms to protect the privacy and confidentiality of individual health information. We recognize that the need to protect patient information is an important aspect of preventing potential abuse, such as segregation or discrimination against patients, however, an additional consequence is that patients are potentially restricted from participating in medical research that may be of benefit to them. The HIA places severe restrictions on access to patient information by researchers, as well as on the ability of anyone other than the patient's physician or approved health information custodian (i.e. pharmacist, hospital board, etc), to contact the patient for any reason, including informing him/her of research opportunities, without prior written consent from the patient. No accommodation or recommendation is made regarding patient groups that may be difficult to access due to compliance with this Act.

The HIA is similar to the US Health Insurance Portability and Accountability Act (HIPAA) (NIH 2004). The HIPAA contains a section specifically addressing access to personal health information for research or for the purpose of recruiting patients into studies. As for the HIA, the only people allowed to contact patients to inform them of potentially relevant research are those who already have access to their health information, including the patient's physician and those employed by a health data collection agency, such as a health plan or health care clearinghouse. Violation of this requirement can only happen if an institutional review board (IRB) has waived this restriction. The restrictive nature of these conditions has been linked to a decline in medical research. In a recent publication by the Infectious Diseases Society of America Research Committee, the authors discuss how 'excessive regulatory oversight' has impacted clinical research, suggesting that HIPAA has had a negative impact on medical research and proposing the removal of research from the activities covered by HIPAA (Burman 2009).

The TriCouncil Policy Statement was jointly prepared by three federal research-funding agencies in Canada, the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council of Canada (SSHRC) (CIHR 1998). This document was based on recognized international research policies and expresses the Agencies' commitment to promoting ethical research on human subjects. This document outlines the procedures that must be followed in order to receive funding from these agencies, including protection of research subject confidentiality and privacy. It goes on to discuss the importance of balancing infringements of privacy against the need for research and states that without access to personal information it would be difficult, if not impossible, to conduct research and that researchers may be justified in accessing personal information in the public interest.

This document also explicitly details the requirement to obtain informed consent from potential research subjects. The only instance where the need for first hand consent is bypassed occurs in cases where the subject is not able to

provide consent as a result of not being mentally competent (i.e. due to illness or very young age) or unconsciousness. The only explicit exception to the need to obtain any prior consent, outlined in the document, is in the case of emergency health situations where time is of the essence and an eligible third party is not available to provide consent. In this situation, as long as certain conditions hold, including that fact that no standard efficacious care exists or the research offers a distinct possibility of greater benefit than standard care, and the risk of harm is not greater than that involved in standard care or the potential benefits clearly outweigh the potential risks, IRB approved research may proceed. Other exceptions that may exist are subject to IRB approval and include situations where the research could not be practically carried out without waiver or alteration of standard consent protocols.

Situations where patients cannot readily be accessed through standard channels (i.e. by the treating physician or other health care agency) and where research would therefore be impractical include those that are time sensitive, as in acute disease. The current sequence of notification starts with the diagnostic lab that notifies treating physicians who, in turn, notify their patients. The two points at which recruitment for research subjects could then occur is at detection, where lab personnel could notify patients that a study potentially relevant to them is available, or at physician notification, where the physician or other office staff could in turn notify the patient. Utilization of these recruitment avenues would require participation of either the lab or the physician. In our study, neither of these avenues was available in that the lab identifying the Monospot positive cases declined to participate (due in part to lack of required infrastructure) and a sufficient number of treating physicians did not agree to participate in research, often citing they were too busy. Potential solutions to these problems include staffing the diagnostic lab with dedicated research personnel who would be responsible for notifying patients of research in a timely manner, and enhancing physician participation in research. Given that neither of these conditions existed at the time of our study, removal of the condition that patients provide written consent in order for research staff to contact them regarding study recruitment,

was sought from our IRB. We argued that the lack of rapid access to mono patients would exclude them from not only receiving the potential benefits of research but in deciding if they would like to participate in the first place. Given that privacy in the absence of research has the potential to hurt patients and society, we propose further examination of these issues in light of the existence of patient populations that are difficult or impossible to access under current policies. The patient right to privacy must be balanced against the right to have research conducted that potentially improves patient health.

The impact of placing restrictions on medical research in certain populations can be examined historically. One well known example is the limitation of studies in children, with the consequence that many of the treatments offered to pediatric patients are 'off label' and have not been adequately tested in this population (Bazzano 2009, Choonara 2002, Karlberg 2009, Lindell-Osuagwa 2009, Park 2008). In more recent times, regulatory bodies have recognized the unintended impact of limiting pediatric research and have reversed this restriction, calling instead for more research in children (Bonetta 2000).

The population we are interested in (mono patients) is composed primarily of adolescents and young adults who are generally otherwise healthy, and due to both the typical health care seeking behavior of this age group and the acute nature of mono, unlikely to be diagnosed or treated in a specific medical centre, or care for by a small group of physicians (especially in large urban centres). In an environment where the ability to contact patients is severely restricted, recruiting subjects for a community study becomes prohibitively complicated and unmanageable. As mono is a condition for which there is no cure and treatment options are limited, this is a population that could benefit from research, and yet our experience was fraught with difficulties in accessing patients, providing a clear example of the contradiction between the Tri-Council Statement and the HIA.

Specifically, according to the Tri-Council Statement, "members of society should not be unfairly excluded from the potential benefits of research participation," such that "individuals in need of research may be denied" the

opportunity. The role of IRB often includes negotiating the balance between patient privacy and the need for research and as such may be increasingly called upon to determine the value of research with respect to the potential benefit to individuals and/or society, and to interpret and manage privacy regulations accordingly in the promotion of such research.

Treatment Results

Feasibility: Although few patients were enrolled in our trial, we were able to demonstrate the feasibility of various trial components. Development of the forms included feedback from the people involved. For example, physicians provided feedback on the physician-related protocols and forms, while acupuncturists provided feedback on the acupuncture-related protocols and forms; patient forms were pre-tested by individuals in our target age group. This may have contributed to the high level of compliance observed for both protocols and outcome measurement tools.

Treatment Details: Our small sample size limits our ability to provide information around the effect of acupuncture on mono, however, some information on treatment parameters was gained. Acupuncture points commonly used for both participants in this group included spleen 6 and 10, stomach 25 and 36, large intestine 11, and heart 7. In addition to acupuncture, other TCM treatments, including cupping and diet and lifestyle recommendations were employed. The number of required treatments differed between participants. Acupuncture participant 1 (Acu1), in conjunction with the practitioner, decided to halt treatment after the 9^{th} session because she felt completely recovered. In contrast, acupuncture participant 2 (Acu2) requested additional sessions as she still felt unwell at the 10^{th} session and the practitioner agreed that she could benefit from additional treatment. As this mirrored what may occur in practice we allowed the extra sessions.

Fatigue: The primary outcome measure, the Chalder Fatigue Questionnaire, has been used in one previous trial of mono for the investigation of a psycho-educational tool (Candy 2004). In this trial of 69 UK participants (mean

age 23 years), baseline mean fatigue scores were similar to those in our trial, 19.7 (SD 4.8) for their intervention group and 19.9 (SD 5.7) for their control group, compared to 21.3 (SD 0.58) for our three patients. In relation to the single control participant, our two acupuncture participants had much better recovery from fatigue.

Quality of Life: Norms for the SF-36 have been obtained for a number of healthy populations (Hopman 2000, Ware 1993) and has been used in previous mono studies (Candy 2004, Katon 1999), providing valuable comparative data for our baseline scores (Table 4.9). Although only available for three participants, the scores for the eight SF-36 domains are well below the norms for the healthy populations. The domain in which the acupuncture patients exhibited larger changes than the control was for role emotional. It would be interesting in future studies to investigate the influence of this intervention in emotional support regardless of changes in physical parameters.

Table 4.9: SF-36 Normative and Infectious Mononucleosis Scores

Domain	Canadian Females N= NR; Age 25-34 yr Mean (SD); Hopman 2000	US Females N=275; Age 18-24 yr Mean (SD); Ware 1993	US Mono Patients *N=144, Mean age 21 yr 51% female; Mean (SD); Katon 1999	Current Trial: Baseline patient data; Mean (SD); Range
PF	90.9 (14.8)	90.2 (20.0)	70.2 (20.4)	50.0 (21.8); 35-75
RP	83.7 (31.4)	84.9 (30.7)	21.9 (30.1)	0 (0); 0
BP	75 (21.6)	82.0 (21.3)	51.1 (24.6)	28.3 (5.5); 22-32
GH	77.9 (15.5)	76.5 (18.7)	68.6 (18.1)	54.0 (5.3); 50-60
V	61.2 (17.3)	59.7 (20.1)	32.5 (19.2)	11.7 (10.4); 0-20
SF	83.7 (21.3)	81.7 (21.0)	48.9 (25.0)	16.7 (7.2); 12.5-25
RE	77.6 (35.3)	78.6 (33.9)	61.8 (41.4)	33.3 (57.7); 0-100
MH	74.1 (16.3)	71.5 (19.4)	65.8 (18.4)	46.7 (6.1); 40-52

*PF = physical functioning, RP = role physical, BP = bodily pain, GH = general health, V = vitality, SF = social functioning, RE = role emotional, MH = mental health

**extracted from graph

Acupuncture Effects: Adverse events such as tiredness, pain, discomfort, bruising, or bleeding at needle sites, and aggravation of an existing condition, occurred, but all were mild and transient. Positive events, such as feeling relaxed and energized, were also reported. All of these events have been reported in the acupuncture safety literature to be common and not unexpected (Macpherson 2005, White 2004).

Incidence Data

As a first step in designing this study, we determined annual incidence rates for mono (based on Monospot positive test results), in the Capital Health Region of Alberta, Canada, for 2003-2007, inclusive, to be 1.11/1000 (95% CI (0.95–3.2)) for all ages combined and 5.46/1000 (95% CI (0.89–10.0)) for the 15-25 year old age group.

In comparison to the few other published studies on population incidence rates of mono, our overall rate is higher. This difference may be partially explained by the different diagnostic criteria upon which the reports were based. Our rate is based on heterophile antibody positive serology from cases referred for lab tests by their physicians due to physical exam results suggestive of mono, similar to Davidson et al. who also reported a rate of 1.0/1000 (Davidson 1970). Another study based their rate on this serology as well as blood count and physical exam, and is lower, at 0.45/1000 (Health 1971). Other factors that may have influenced our rate include the accuracy of both the numerator (Monospot positive count) and the denominator (population count). Inflation of the numerator may have occurred due to inclusion of false positives, since the Monospot test has a reported sensitivity of 94% (Meridian Bioscience 2004) and our Monospot test results were not validated by other means (i.e. IgM VCA results). Examination of our Monospot data showed that only 10.3% of Monospot positive cases were verified by an IgM VCA test. Our rate may also have been affected by the possible inclusion of cases residing in other health regions, although exploration of the robustness of our rate demonstrated that even if 20% of the positive cases resided in another region, our rate remained close to 1.0/1000.

Candy et al. reported a mono rate of 0.7/1000 in UK primary care, while other studies in the UK and the US have reported rates ranging between 0.44/1000 and 1.0/1000 (Candy 2002, Davidson 1970, Heath 1972, Hobson 1958). The author of one of the few other multi-year studies discussed limitations in mono testing practices in place during the time period of his study and presented evidence from a detailed sub-study of two clinics that indicated that the true rate in his area was closer to 1.0/1000 (Davidson 1970).

Our data are consistent with other studies in that the highest incidence occurred for older teenagers and young adults. Although no clear temporal trends were identified within each year, consistent with previous studies (Davidson 1970, Evans 1950, Heath 1972, Hobson 1958), our date showed small but statistically significant changes in rates of Monospot positive cases in recent years (2006 and 2008). This is likely due to the increase in March 2006 and the dramatic decrease in Oct 2008 that are apparent in Figures 4.2 and 4.3, however, information to explain these changes is not available.

Our calculation of local mono incidence rate was limited due to the post-hoc nature of the calculation. The intention of gathering this data was to ensure that the local mono population was large enough to make a clinical trial feasible. Had we intended to calculate incidence rates we would have collected all required variables, including patient residency, in order to make our estimates as accurate as possible. A second limitation is that there is currently no dedicated resource for researchers to access health-related patient data in Alberta, even for the most basic determination of disease incidence. Our information was obtained from requests to the Sunquest database data management services, however, compliance with requests were limited by the size of the request (i.e. number of variables and time frame of interest) and whether the technicians had time to complete them. It was not unusual for some requests to be delayed by months or years and no time estimate is provided at the time the request is placed, limiting the usefulness of this process. Many Alberta-based researchers are forced to investigate populations outside of Alberta due to the limited access to local information, which reduces the generalizability of their results to local populations.

4.6 Conclusions

This study provides the first report of mono incidence rates for a Canadian population, with an annual rate of approximately 1/1000, showing that mono is not a rare condition in this region. Conventional medical treatment options for mono are limited and research into novel treatment options have been scarce. We designed and piloted the first RCT of acupuncture for mono and demonstrated the feasibility of the protocol in a small number of patients.

Our major limitation was in accessing mono patients for the trial. This study highlights an important barrier to clinical research that currently exists in, but is not restricted to, Alberta, Canada, especially in under-studied populations - the strict limitations in contacting patients in order to inform them of research studies that may be of interest and benefit to them.

Because mono is not a reportable disease and because the condition is perceived as mild and transient, patient care is generally carried out not in designated clinics but by community physicians whose practice infrastructures may make it very difficult to recruit patients for research. Current restrictions in directly contacting patients funnel recruitment through these practitioners or to indirect patient contact methods such as media advertisements, however, researchers interested in the acute phase of mono, and other infections, may not find this method feasible due to time limitations imposed by the natural progression of the infection.

While this study highlights the difficulty in recruiting patients with mono, it is likely that it is also a problem for research in other conditions for which care is mainly provided by community physicians, especially in cases where primary care is provided at walk-in clinics rather than in settings where long-term patient-practitioner relationships exist, a phenomenon that is becoming increasingly common, especially for generally healthy individuals.

It seems that otherwise healthy adolescents and young adults have replaced children in becoming the new “orphan” population, for which research is challenged. This phenomenon is exacerbated by infrequent contact with health care providers for wellness care and the rare rates of illness in these age groups.

For illnesses such as mono, that may require only a single point of contact around diagnosis, it limits the effectiveness of "usual" recruitment methods through health care facilities or health care providers. If research is to be done to help identify more effective treatments, then the right to privacy must be challenged by the right to conduct relevant research that serves the public good. In our case, for example, diagnostic labs were not able to invite patients to consider participating based on their positive test results, suggesting that we are somehow protecting patients from the opportunity to participate in research (when in fact, ethical guidelines for research in humans suggest that the opposite is true – that research benefits humans and people should not be unduly deprived of the opportunity to participate). Given the current restrictions on direct patient contact, a key feature of a follow up study in mono would include obtaining buy in from health care organizations and physicians, who see many potentially eligible patients, in order to ensure notification of patients in a timely fashion and recruitment of suitable study populations.

4.7 Reference List

Alberta Health and Wellness (AHW). *Health Information Act*. Edmonton, AB: Alberta Queen's Printers, 1999.

Alberta Health and Wellness (AHW). *Interactive Health Data Application*. www.ahw.gov.ab.ca/IHDA_Retrieval/selectSubCategoryParameters.do# (Accessed Jan 2010).

Anastasi J, McMahon D. Testing strategies to reduce diarrhea in persons with HIV using traditional Chinese medicine: acupuncture and moxibustion. *Journal of the Association of Nurses in AIDS Care.* 2003;14(3):28-40.

Andersson J, Britton S, Ernberg I, Andersson U, Henle W, Sköldenberg B et al. Effect of acyclovir on IM: a double blind, placebo controlled study. *Journal of Infectious Diseases*. 1986;153(2):283-290.

Andersson J, Sköldenberg B, Ernberg I, Britton S, Henle W, Andersson U. Acyclovir treatment in primary Epstein-Barr virus infection. A double-blind placebo-controlled study. *Scandinavian Journal of Infectious Diseases*. 1985;47(Suppl):107-115.

Andersson J, Sköldenberg B, Henle W, Giesecke J, Ortqvist A, Julander I et al. Acyclovir treatment in IM: a clinical and virological study. *Infection*. 1987;15(Suppl 1):S14-20.

Aune A, Alraek T, Lijua H, Baerheim A. Acupuncture in the prophylaxis of recurrent lower urinary tract infection in adult women. *Scandinavian Journal of Primary Health Care*. 1998;16:37-39.

Avins A. Can unequal be more fair? Ethics, subject allocation and randomised clinical trials. *Journal of Medical Ethics.* 1998;24:401-408.

Balk E, Bonis P, Moskowitz H, Schmid C, Ioannidis J, Wang C, Lau J. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA.* 2002;287:2973-82.

Bazzano AT, Mangione-Smith R, Schonlau M, Suttorp MJ, Brook RH. Off-label prescribing to children in the United States outpatient setting. *Academic Pediatrics*. 2009;9(2):81-88.

Beal M, Nield-Anderson L. Acupuncture for symptom relief in HIV-positive adults: lessons learned from a pilot study. *Alternative Therapies in Health and Medicine.* 2000;6(5):33-42.

Benson K, Hartz A. A comparison of observational studies and randomized, controlled trials. *New England Journal of Medicine.* 2000;342:1878-1886.

Bender CE. The value of corticosteroids in the treatment of IM. *Journal of the American Medical Association*. 1967;199(8):529-31.

Blackwood B. Methodological issues in evaluating complex healthcare interventions. *Journal of Advanced Nursing*. 2006;54(5):612-622.

Bolden KJ. Corticosteroids in the treatment of IM. *Journal of the Royal College of General Practitioners*. 1972;22(115):87-95.

Bonetta L. Pediatric study of medicines becomes mandatory. *Nature Medicine*. 2000;6(10):1069.

Borund E, Alraek T, White A, Fonnebo V, Grimsgaard S. The effect of TCM acupuncture on hot flushes among menopausal women (ACUFLASH) study: a study protocol of an ongoing multi-centre randomised controlled clinical trial. *BMC Complementary and Alternative Medicine.* 2007;7(6);doi:10.1186/1472-6882-7-6.

Boutron I Tuback F, Giraudeau B, Ravaud P. Blinding was judged more difficult to achieve and maintain in non-pharmacological than pharmacological trials. *Journal of Clinical Epidemiology.* 2004;57:543-550.

Buchwald D, Pearlman T, Umali J, Schmaling K, Katon W. Functional status in patients with chronic fatigue syndrome, other fatiguing illnesses, and health individuals. *The American Journal of Medicine*. 1996;101:364-370.

Buchwald D, Rea T, Katon W, Russo J, Ashley R. Acute infectious mononucleosis: characteristics of patients who report failure to recover. *American Journal of Medicine.* 2000;109:531-537.

Burman W, Daum R, for the Infectious Diseases Society of America Research Committee. Grinding to a halt: the effects of the increasing regulatory burden on research and quality improvement efforts. *Clinical Infectious Diseases*. 2009;49:328-335.

Cabioglu MT, Cetin BE. Acupuncture and immunomodulation. *American Journal of Chinese Medicine*. 2008;36(1):25-36.

Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERC), Social Sciences and Humanities Research Council of Canada (SSHRC). *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 1998* (with 2000, 2002 and 2005 amendments).

Candy B, Chalder T, Cleare A, Peakman A, Skowera A, Wessely S, et.al. Predictors of fatigue following the onset of infectious mononucleosis. *Psychological Medicine.* 2003;33:847-855.

Candy B, Chalder T, Cleare A, Wessely S, Hotopf M. A randomised controlled trial of a psycho-educational intervention to aid recovery in infectious mononucleosis. *Journal of Psychosomatic Research.* 2004;57(1):89-94.

Candy B, Chalder T, Cleare A, Wessely S, Hotopf M. What advice do patients with infectious mononucleosis report being given by their general practitioner? *Journal of Psychosomatic Research*. 2005;58:435-437.

Candy B, Chalder T, Cleare AJ, Wessely S, Hotopf M. What advice do patients with infectious mononucleosis report being given by their practitioner? *Journal of Psychosomatic Research.* 2005;58:435-437.

Candy B, Chalder T, Cleare AJ, Wessely S, White P, Hotopf M. Recovery from infectious mononucleosis: a case for more than symptomatic therapy? A systematic review. *British Journal of General Practice.* 2002;52:844-851.

Ceccherelli F, Gagliardi G, Rossato M, Giron G. Variables of stimulation and placebo in acupuncture therapy. *Journal of Alternative and Complementary Medicine.* 2000;6:275-279.

Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, Wallace E. Development of a fatigue scale. *Journal of Pychosomatic Research.* 1993;37(2):147-153.

Chalmers T, Celano P, Sacks H, Smith H. Bias in treatment assignment in controlled clinical trials. *New England Journal of Medicine.* 1983;309:1358-1361.

Chang BH, Boehmer U, Zhao Y, Sommers E. The combined effectof relaxation response and acupuncture on quality of life in patients with HIV: a pilot study. *Journal of Complementary and Alternative Medicine*. 2007;13(8):807-815.

Chen J, Chen M, Wang Y. Effects of acupuncture on the immunological functions in hepatitis B virus carriers. *Journal of Traditional Chinese Medicine.* 1999;19(4):268-272.

Cho H, Costa E, Menezes P, Chalder T, Bhugra D, Wessely S. Cross-cultural validation of the Chalder Fatigue Questionnaire in Brazilian primary care. *Journal of Psychosomatic Research.* 2007;62:301-304.

Choonara I, Conroy S. Unlicensed and off-label drug use in children. Implications for safety. *Drug Safety*. 2002;25(1):1-5.

Dumville J, Hahn S, Miles J, Torgerson D. The use of unequal randomization ratios in clinical trials: a review. *Contemporary Clinical Trials.* 2006;27:1-12.

Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technology Assessments*. 2003;7:1-76.

Ezzo J, Berman B, Hadhazy V, Jadad A, Lao L, Singh B. Is acupuncture effective for the treatment of chronic pain? *Pain.* 2000;86:217-225.

Government of Alberta. *Official Population Lists*. www.municipalaffairs.alberta.ca/mc_official_populations.cfm (Accessed Jan 2010).

Health Canada. *Guidelines for Reporting Adverse Reactions to Marketed Drugs.* 2001. www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2001-guide-ldir_indust/index-eng.php (Accessed Sept 15, 2009).

Hopman W, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S, Berger C et al. Canadian normative data for the SF-36 health survey. *Canadian Medicial Association Journal*. 2000;163(3):265-271.

Ioannidis J, Haidich A, Pappa M, Pantazis N, Kokori S, Tektonidou M, et.al. Comparison of evidence of treatment effects in randomizd and non-randomized studies. *Journal of the American Medical Association.* 2001;286:821-830.

Jadad A. *Randomized Clinical Trials: A Users Guide*. London, UK: BMJ Books, 1998 p32.

Johannsen E, Schooley RT, Kaye K. Epstein-Barr virus (infectious mononucleosis), In Mandell, Douglas, and Bennett's *Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia, PA: Churchill Livingstone, 2005 p1801–1820.

Juni P, Egger M. Letter to the editor. *Journal of the American Medical Association.* 2002;288(19):2407-2408.

Joos S, Schott C, Zou H, Daniel V, Martin E. Immunomodulatory effects of acupuncture in the treatment of allergic asthma: a randomized controlled study. *Journal of Alternative and Complementary Medicine*. 2000;6(6):519-525.

Kaptchuk T. Acupuncture: theory, efficacy and practice. *Annals of Internal Medicine.* 2002;136:374-383.

Karlberg J. Clinical trial subject characteristics – ages and gender. *Clinical Trial Magnifier*. 2009;2(9):456-471.

Katon W, Russo J, Ashley R, Buchwald D. Infectious mononucleosis: psychological symptoms during acute and subacute phases of illness. *General Hospital Psychiatry*. 1999;21:21-29.

Kawakita Shichidou T, Inoue E, Nabeta T. Preventive and curative effects of acupuncture on the common cold: a mulitcentre randomized controlled trial in Japan. *Complementary Therapies in Medicine.* 2004;12:181-188.

Khan K, Daya S, Collins J, Walter S. Empirical evidence of bias in infertility research: overestimation of treatment effect in crossover trials using pregnancy as the outcome measure. *Fertility and Sterility.* 1996;65(5):939-945.

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine*. 2001;135-982-989.

Kunz R, Oxaman A. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ.* 1998;317:1185-1190.

Lewis G, Pelosi A, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychological Medicine.* 1992;22:465-486.

Lin YC, Bioteau AB, Ferrari LR, Berde CB. The use of herbs and complementary and alternative medicine in pediatric preoperative patients. *Journal of Clinical Anesthesia*. 2004;16(1):4-6.

Linde K, Witt C, Streng A, Weidenhammer W, Wagenpfeil S, Brinkhaus B et al. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain.* 2007;128:264-271.

Lindell-Osuagwu L, Korhonen MJ, Saano S, Helin-Tanninen M, Naaranlahti T, Kokkis H. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. *Journal of Clinical Pharmacy and Therapeutics*. 2009;34:277-287.

Lu W, Hu D, Dean-Clower E, Doherty-Gilman A, Legedza AT, Lee H et al. Acupuncture for chemotherapy-induced leukopenia: exploratory meta-analysis of randomized controlled trials. *Journal of the Society for Integrative Oncology*. 2007;5(1):1-10.

Lu W, Matulonis UA, Doherty-Gilman A, Lee H, Dean-Clower E, Roseluk A et al. Acupuncture for chemotherapy-induced neutropenia in patients with gynecologic malignancies: a pilot randomized, sham-controlled clinical trial. *Journal of Alternative and Complementary Medicine*. 2009;15(7):745-753.

MacPherson H. Pragmatic clinical trials. *Complementary Therapies in Medicine.* 2004;12:136-140.

MacPherson H, Thorpe L, Thomas K, Campbell M. Acupuncture for low back pain: traditional diagnosis and treatment of 148 patients in a clinical trial. *Complementary Therapies in Medicine.* 2003;12:38-44.

Medical Research Council (MRC). *A Framework for Development and Evaluation of RCTs for Complex Interventions to Improve Health*. Medical Research Council, 2000.

Meridian Bioscience Europe. *Monospot*. Cincinnati, OH: Meridian Bioscience, Inc. 2004.

Moher D, Pham B, Jones A, Cook D, Jadad A, Moher M et al. Does quality of reports of randomised trials affect estimates of intervention effect reported in meta-analyses? *Lancet*. 1998;352(9128):609-613.

National Institutes of Health (NIH). *Clinical Research and the HIPAA Privacy Rule*. NIH, 2004.

Park S, Grayson M. Clinical Research: protection of the ‘vulnerable”? *Journal of Allergy, and Clinical Immunology*. 2008;121:1103-1107.

Paterson C, Britten N. Acupuncture as a complex intervention: a holistic model. *Journal of Alternative and Complementary Medicine.* 2004;10(5):791-801.

Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. *BMJ.* 2005;330:1202-1205.

Pocock S. Allocation of patients to treatment in clinical trials. *Biometrics.* 1979;35:183-197.

Price S, Lewith G, Thomas K. Acupuncture care for breast cancer patients during chemotherapy: a feasibility study. Integrative *Cancer Care.* 2006;5(4):308-314.

Prout C, Dalrymple W. A Double blind study of 82 cases of IM treated with corticosteroids *Journal of the American College Health Association*. 1966;15(1):62-66.

Rea T, Russo J, Katon W, Ashley R, Buchwald D. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr Virus. *Journal of the American Board of Family Practice.* 2001;14:234-242.

Roy M, Bailey B, Amre DK, Girodias JB, Bussières JF, Gaudreault P. Dexamethasone for the treatment of sore throat in children with suspected IM. *Archives of Pediatric and Adolescent Medicine*. 2004;158(3):250-254.

Salter G, MacPherson H. Acupuncture for chronic neck pain: a pilot for a RCT. *BMC Musculoskeletal Disorders.* 2006;7:99.

Schulz K, Chalmers I, Hayes R, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association.* 1995;273:408-412.

Schulz K, Grimes D. Blinding in randomised trials: hiding who got what. *Lancet.* 2002;359:696-700.

Singer L, Karakis I, Ivri K, Gross M, Bolotin A, Gazala E. Characteristics of complementary and alternative medicine use by parents of asthmatic children in Southern Israel. *Acta Paediatrica*. 2007;96:1693-1697.

Spigelblatt L, Laine-Ammara G, Pless B, Guyver A. The use of alternative medicine by children. *Pediatrics*. 1994;94:811-814.

Thomas K, MacPherson H, Thorpe L, Brazier J, Fitter M, Campbell M, Roman M et al. Randomized controlled trial of a short course of traditional acupuncture compared with usual care for persistent non-specific low back pain. *BMJ.* 2006;333(623):dol:10.1136/bmj.38878.907361.7C.

Torgerson D, Klaber-Moffett J, Russell I. Patient preferences in randomized trials: threat of opportunity. *Journal of Health Services, Research and Policy*. 1996;1(4):194-197.

Torre D, Tambini R. Acyclovir for treatment of IM: a meta-analysis. *Scandinavian Journal of Infectious Diseases*. 1999;31(6):543-7.

Tunis S, Stryer D, Claney C. Practical Clinical Trials. *Journal of the American Medical Association.* 2003;290:1624-1632.

Tynell E, Aurelius E, Brandell A, Julander I, Wood M, Yao QY et al. Acyclovir and prednisolone treatment of AIM: a multicenter, double blind, placebo controlled study. *Journal of Infectious Disease*s. 1996;174(2):324-331.

van der Horst C, Joncas J, Ahronheim G, Gustafson N, Stein G, Gurwith M, Fleisher G, Sullivan J, Sixbey J, Roland S et al. Lack of effect of peroral acyclovir for the treatment of AIM. *Journal of Infectious Disease*s. 1991;164(4):788-792.

Vendelbo Johansen L, Lildholdt T, Bende M, Toft A, Brahe Pedersen C, Danielsson GP. IM treated by an antihistamine: a comparison of the efficacy of ranitidine (Zantac) vs placebo in the treatment of IM. *Clinical Otolaryngology*. 1997;22:123-125.

Ware J. SR-36 *Health Survey Manual: An Interpretation Guide*. Boston, MA: The Health Institute, New England Medical Centre, 1993.

Ware JE, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Lincoln, RI: Quality Metric Inc, 1993.

White A, Filshie J, Cummings T. Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complementary Therapies in Medicine.* 2001;9:237-245.

White P, Thomas J, Sullivan P, Buchwald D. The nosology of sub-acute and chronic fatigue syndromes that follow infectious mononucleosis. *Psychological Medicine.* 2004;34:499-507.

Wood L, Egger M, Gludd L, Schulz K, Juni P, Altman D et al. Epirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ*. 2008;336(7644):601-605.

Zan-Bar T, Aron A, Shoenfeld Y. Acupuncture therapy for rheumatoid arthritis. *Journal of Rheumatology*. 2004;7:207-214.

Chapter 5: Summary, Conclusions, and Implications

5.1 Statement of Study Purpose

The purpose of this dissertation was to explore the intersection of traditional Chinese medicine (TCM) and fatigue, and more specifically, TCM acupuncture and infectious mononucleosis (mono). This research could have been carried out in one of two ways. In the first way, evidence from past clinical studies could have been synthesized (i.e. through a systematic review (SR)) and used to inform the development of a more rigorous study (i.e. a randomized controlled clinical trial (RCT)), which would in turn inform clinical practice. The second way takes the opposite approach in that it looks at a novel clinical practice and asks if this approach is effective. A SR of the practice would demonstrate that the question of effectiveness had not yet been addressed through clinical research and the logical next step would then be to design a pilot trial to begin to answer this novel question.

It is this second pathway that this body of work pursued. With the knowledge that mono is treated by some practitioners with acupuncture alone, we proceeded to explore the knowledge base behind this, and when found to be lacking, we choose to contribute to it through the development and conduct of a clinical trial. Where information directly related to our topic of interest, acupuncture treatment of mono, was limited, we attempted to compensate by broadening our searches to related topics. For example, when a preliminary examination of the literature indicated that information on TCM treatment of mono was sparse we extended our interests to include TCM treatment of other conditions for which fatigue was a dominant symptom. We first considered searching for TCM treatment of fatigue in other viral infections. A search of English-language databases showed that information about the effect of TCM specifically on fatigue was lacking. We considered extending the search to Chinese-language databases, however, consultation with colleagues in China on searching for viral-related fatigue revealed that, due to the way these concepts translated into Chinese and were indexed, a literature review of this topic was not

feasible. We then decided to focus on a condition for which fatigue was the predominant symptom, chronic fatigue, and which has also been linked to mono. The first part of our research consisted of a series of three SRs that were intended to inform the second part, the development and conduct of a pilot RCT of acupuncture for mono.

The first two SRs were designed to examine the efficacy of TCM therapies for mono and chronic fatigue, however, methodological issues around the quality of clinical research, primarily in China, dominated the focus of the reviews. The third SR was intended to extend the acupuncture safety evidence beyond the current adult-focused reviews into pediatric populations. Literature on this topic was identified and synthesized into an estimate of adverse event (AE) incidence in pediatric acupuncture.

The RCT was successfully designed and each element piloted. Due to limitations in recruitment, however, only three patients participated in the trial. The primary effect of the small sample size was to limit the determination of parameters related to treatment effect, however, successful implementation of other elements is informative to further research in this area. In addition, during the process of establishing our mono population, local incidence data was collected and summarized. This information complements existing data and provides the first publication of population-based mono incidence in Canada.

5.2 Summary of Methods

This doctoral work employed four main procedures. First, systematic review methodology for efficacy was applied to the topics of TCM in mono and chronic fatigue. Ten English-language and two Chinese-language databases were searched, from inception to 2008, for RCTs of TCM interventions for either mono or chronic fatigue. Acceptable control groups were placebo, sham, no treatment, standard of care (SOC), or an active control previously shown to be effective for mono or chronic fatigue. After initial screening of titles and abstracts, potentially relevant publications were retrieved and assessed for inclusion. No language restrictions were applied.

The key methodology employed in this project was searching for efficacy data using hypothesis testing/proving methods. It was known that TCM therapies are used in practice for both mono and chronic fatigue, however, the efficacy of TCM in these conditions had not yet been reported. In focusing on efficacy we restricted searches to RCTs, a design that, by attempting to limit sources of bias, is known to provide the best estimate of effect of an intervention.

Second, systematic review methodology for safety was applied to the topic of needle acupuncture in children. We chose to limit the scope of this review to needle acupuncture because that was intervention of choice for our RCT. In addition, as the most commonly practiced form of acupuncture, adult safety data is generally focused on this procedure. A total of 18 English-language databases were searched, from inception to June 2007. After screening of titles and abstracts, potentially included articles were assessed for inclusion. No language restrictions were applied. Safety data were extracted from all included studies.

In contrast to the SRs for efficacy, this SR was intended to be hypothesis generating. Much is known about AEs in adult acupuncture, thus safety reviews are able to focus on specific events. In the application of acupuncture to children, however, AEs have been, thus far, poorly defined. Searches for information on AEs, in this context, need to be broad and general (Loke 2007). RCTs are known to underestimate rare harms due to relatively small sample size, restricted populations, interventions that do not necessarily reflect actual practice, and limited time frame for both intervention and follow-up (Egger 2001, Ioannidis 2004). Other study designs, such as observational studies, that follow large populations over long time periods, and prospective audits of clinics, may serve as valuable additions to the collection of AEs, especially those that are rare or occur in actual practice rather than in a controlled setting. In turn, case reports may be useful in identifying novel, serious, or rare AEs.

Third, a variety of epidemiological skills were applied to the development and conduct of a pragmatic parallel group randomized controlled trial (RCT). This trial was originally intended to evaluate TCM as a whole system, in that patients would be randomized to conventional care (as practiced by community

physicians) or TCM (as practiced by community TCM providers), which may have included any or all TCM therapies. When we investigated the feasibility of this approach we learned that, due to regulations around provision of herbal therapies in research studies, approvals may take years to obtain, and decided to restrict the intervention to acupuncture therapy. In this trial we brought the application of a pragmatic acupuncture RCT to the area of mono, for the first time. Our primary outcome was feasibility, as measured by success of recruitment, protocol compliance, and completion of outcome measures, and change in fatigue over time. While we had also hoped to capture information on the development of chronic fatigue, the expected sample size and time frame available for this study were unsuitable for this purpose.

Fourth, examination and manipulation of population data regarding the epidemiology of mono in the Capital Health Region (CHR) was carried out. Data retrieval involved obtaining information on Monospot positive patients in the CHR, for the years 2003-2008, from a central database. Data on these patients, including gender, age, date of test, and collection location was summarized using descriptive statistics and displayed graphically. Chi-square tests and Poisson regressions were used to investigate associations between variables such as age, gender, and change in incidence over time.

5.3 Summary of Major Findings and Limitations

5.3.1 Systematic reviews of traditional Chinese medicine for infectious mononucleosis and chronic fatigue

5.3.1.1 Infectious mononucleosis

No studies of any design, or indeed, any information on TCM treatment of mono, were found through the English-language database searches. Searches of the Chinese-language databases showed that some articles on the treatment of and a limited number of studies have been published in the Chinese medical literature. Although these articles were published as RCTs, verification of randomization

methods through author interview determined that none of these studies truly used randomization and that most were simply practice summaries comparing different treatments over long time periods.

5.3.1.2 Chronic fatigue

Searches of the English-language databases identified a small number of studies, while searches of the Chinese-language databases were more fruitful. Despite finding studies of TCM for chronic fatigue syndrome that were described as RCTs, verification of randomization methods through author interview determined that few studies actually used randomization. The small number that did randomize the patients used comparison groups that were invalid for our review, comparing two active treatments, neither of which had previously been shown through clinical research to be effective in chronic fatigue. All the studies that were identified had been conducted in China.

5.3.1.3 Methodological considerations

Methodological considerations, such as the choice of condition to study, inclusion of language-other-than-English (LOE) databases in search strategies, and verification of the methods used in RCTs, directly impacted our SR results. The choice of condition to study was influenced by the ability to effectively search for the condition in all databases, English or Chinese. Although we were able to search for infectious mononucleosis, the more general topic of viral-related fatigue was not feasible, as it would have required searching for every virus of interest separately. In addition, the concepts of fatigue are expressed differently in Chinese, especially in relation to traditional Chinese medicine, which would have impacted both on the utility of the search results and the similarity in research questions and results between the English and Chinese searches. As an example of the difference in search results, searching for randomized or controlled clinical trials combined with fatigue and virus or viral infection in standard English-language databases produced 4116 references, while

a similar search of the Chinese-language databases produced over 120 000 references.

The effect of including Chinese-language databases was to increase the numbers of potentially included studies from 0 to 14 (mono SR) and from 8 to 36 (chronic fatigue SR). When authors were interviewed regarding their methods of patient assignment to groups, it was found that few studies actually used randomization. Preferred methods of patient assignment included alternation and patient choice.

5.3.1.4 Limitations

The SRs of mono and CF were limited to RCTs due to the potential of this design to minimize bias and potentially provide the most accurate estimates of treatment effect. This is not to suggest that other study designs, such as non-randomized controlled clinical trials (CCTs), do not have merit, however, for studies of efficacy, RCTs are recommended as the best source of evidence. During the conduct of these SRs we determined that most of the studies labelled as RCTs were in fact CCTS, in that they used alternation to assign patients to groups. The decision to limit to RCTs was influenced by the prior knowledge that many studies conducted and published in China suffer from lack of reporting and do not include information on characteristics of participants or baseline measures, making it impossible to determine the potential influence of bias on study results.

5.3.2 Systematic review of the safety of pediatric acupuncture

5.3.2.1 Adverse events of acupuncture technique versus system of care

Given that acupuncture may be investigated as a technique or as a system of care, it is worth mentioning here that the literature around acupuncture AEs has not yet included discussion of the differences between AEs associated with acupuncture as a technique or as a system. Our examination of published reports shows that the AEs mentioned are most often those that are thought to be specific to the technique, such as pain or bleeding at puncture sites rather than AEs that

may be more generally related to the overall experience of acupuncture therapy, such as delayed diagnosis or failure to obtain necessary conventional medical care. We evaluated all reports of AEs in acupuncture studies, regardless of context.

5.3.2.2 Pediatric acupuncture adverse events

This was the first known SR of the safety of needle acupuncture in children. We identified six serious and 133 mild AEs that were rated as possibly, probably, or certainly caused by the acupuncture treatment. The serious AEs included one case each of cardiac rupture, pneumothorax, nerve impairment, and three cases of infection. This data supports the low frequency of serious AEs reported for adults and that occurrence is often related to technical error rather than inherent to the procedure itself. Overall low numerator and denominator values limited true determination of pediatric AE incidence, however, we report incidence of mild AEs of 103/1327 patients (7.8% 95% CI: (6.3 – 9.2)) and 103/13629 treatment sessions (0.76% 95% CI (0.61 – 0.90)). We were unable to estimate risk of serious harm, as the reports of serious AEs were limited to case reports.

The only other pediatric-specific measure of acupuncture AEs reported an incidence of 29/1865 treatment sessions (1.6%), however, this review included only RCTs and was limited by other methodological factors (Jindal 2008). In contrast, we included all study designs and the majority of the AEs we identified were from non-randomized studies (34 from RCTs, 91 from cohort studies, and 14 from case reports).

5.3.2.3 Categorization of acupuncture adverse events

Upon reviewing the literature on the safety of acupuncture, we noted that many systems for categorizing acupuncture AEs are in use. This results in difficulty in making comparisons between studies and limits synthesis of data. Development and implementation of a standardized system for collecting, categorizing, and reporting acupuncture AEs would enhance the current safety

research efforts. With the increasing popularity of studies examining acupuncture as a complex intervention or whole system, specifying if the AEs are related to the technique or other aspects of the experience should be considered.

5.3.2.4 Need for pediatric studies

Utilization studies have shown that acupuncture is commonly used by children (Barnes 2008, Lin 2004, Singer 2007, Spiegelblatt 1994) and that children are included in acupuncture research studies (Adams 2005). Addition of pediatric data to the safety literature could be accomplished in one of two ways, by full reporting of safety information in pediatric research reports and by including children in large-scale prospective practice audits and surveys. Both sources of information have been valuable in determining risk estimates in adult acupuncture and should be strongly encouraged in pediatric acupuncture.

5.3.2.5 Limitations

Although the SR of TCM for pediatric acupuncture included non-English articles, we did not specifically search non-English databases, as we had not established the collaborations that would allow us to do this at the time of this study. It has been shown that most Chinese-language journals are not indexed in standard databases, such as MEDLINE and Embase (Fung 2008, Xia 2008), thus we may have missed some relevant Chinese articles, and as this problem is not limited to Chinese journals (Pilkington 2005), relevant articles in other languages as well. SRs of the Japanese acupuncture AE literature have been published and made available in English (Yamashita 2001). We commend these efforts and encourage authors in other countries to synthesize and widely publish their literature, in this and other fields of research. Although isolated researchers are beginning to publish information specifically on safety (Leung 2009), to our knowledge, a comprehensive synthesis of the Chinese literature on acupuncture safety has not yet been published (Chinese Cochrane Centre, personal communication). Given that reporting of AEs in Chinese TCM trials has been shown to be greatly limited (Tang 1999), we question whether a systematic

review of Chinese acupuncture trials would be a worthwhile endeavour at this time.

5.3.3 Development and conduct of a pilot RCT of acupuncture for infectious mononucleosis

5.3.3.1 Development of trial

Due to the sparcity of published information related to acupuncture treatment parameters specifically for mono, we accessed other related sources of information, including personal communications with TCM experts and practitioners, other trials of acupuncture, and other trials of conditions involving infection and or fatigue. As TCM acupuncture treatment is based less on the underlying cause and more on presentation of symptoms, treatment details for similar symptoms may be informative in developing guidelines for less well-documented conditions, such as mono.

5.3.3.2 Physician recruitment

Physician recruitment was considered to be a key element to the success of this study and was begun well in advance of the trial start date. Actual trial recruitment was carried out by 14 physicians, eight in private practice and six in walk-in settings. Most of the physicians that declined to participate did so due to insufficient numbers of mono cases in their practices. It is interesting to note that out of the 53 negative responses, only two indicated that they were not supportive of an acupuncture intervention.

We began our recruitment of physicians based on the assumption that those who were frequent users of the Monospot test would see large numbers of mono cases, however, we found that use of the Monospot test was not an accurate indicator of mono cases. In one extreme case, a physician who used the test over 200 times per year had less than six mono cases per year. It seems that use of the Monospot test in practice is often as a method of excluding mono as a diagnosis.

Once this was known, we based our recruitment process on physicians and clinics that saw large numbers (>20/year) of Monospot positive cases.

5.3.3.3 Participant recruitment

Based on the Capital Health Region Monospot positive data for 2006-2008, our six walk-in clinics together saw approximately seven cases per month, in our age range. It was expected then that we would identify 84 potentially eligible patients. In fact, during our one-year recruitment period, the participating physicians identified 24 mono cases, of which only 17 were eligible for the study. After being informed of the study, three patients (18%) consented and were enrolled. The much lower than expected identification of mono cases may have been influenced by the fact that only one physician in each of the six clinics agreed to recruit patients and that although they attempted to identify all cases in their clinics, this process may not have been very effective and cases were likely missed by the recruiting physician.

5.3.3.4 Piloting of trial

As this was the first RCT of acupuncture for mono, piloting of various components of the trial was an important objective.

a) The protocol for this trial was submitted to our local Research Ethics Board (REB) for approval, who were generally satisfied and had few concerns, especially in relation to the acupuncture intervention. Some REBs are unfamiliar with complementary and alternative medicine and may be expected to be hesitant in their approvals, however, we did not experience this;

b) Once eligible patients were identified, they went through the enrolment process, which involved informed consent and baseline measures. These procedures were performed without any difficulties during the trial. The completion of follow-up measures was also generally well done, in that all weekly forms were completed an returned in a timely fashion, with the exception of the control participant who stopped returning forms at week 10;

c) Outcome measurement forms and procedures were based primarily on previously developed and tested materials (i.e. CFQ, SF-36), with the exception of the mono symptom scale. No single tool for this assessment is available. Authors of other mono studies have either modified pre-existing tools or simply used their own unpublished tool. In order to be consistent with the format and language of other tools we used, we based the format of this tool on the SF-36 and combined rating scales from the SF-36 with common mono symptoms (Johannse 2005, Rea 2001). There were no problems reported in relation to use of this tool, however, further testing in a larger sample would be needed to determine psychometric properties such as reliability and validity;

d) Protocols for the acupuncture intervention were developed in conjunction with experts in the field and the practitioners selected for this trial. No deviations from the final protocol or difficulties with forms were reported.

e) No difficulties in the conduct of the actual study were reported by other study personnel, including the study coordinator.

5.3.3.5. Informing future research

We had hoped to be able to add to the acupuncture knowledge base information specific to the effect on mono. Due to the difficulties we encountered in recruiting our target population we were unable to gather these data. Future studies may wish to focus on populations that are more readily accessible (i.e. do not require access through a community physician) unless changes are made to privacy legislation that currently restricts recruitment of human subjects.

With regards to the objective of collecting information that may inform further research in this area, we had hoped to contribute to identification of TCM diagnoses common to mono and identification of acupuncture points commonly used in mono treatment. Both of these bodies of information would be important in developing methods for acupuncture research and practice. TCM acupuncture has historically practiced individualized treatment, in that point selection is based on the diagnosis of each patient and may be different for every patient. Identifying whether common diagnoses exist may be an important first step in developing

treatment guidelines, whether for practice or research. A recent development in acupuncture research is the semi-standardization of treatment protocols, wherein certain points are used for each patient, while allowing the practitioner to select additional points as needed.

A second area of acupuncture research that is undergoing methodological development is that of control acupuncture treatments. Current methods include attachment of adhesive needles above acu-points. As some points are not suitable for this procedure (i.e. occur in areas of excess hair or on sharp angles), it is important to identify if points common to mono are amenable to control needles. Although we identified diagnoses and common acu-points between our two acupuncture participants the sample size was too low to make this information truly meaningful to larger numbers of patients.

5.3.3.6 Limitations

The usefulness of our RCT in informing future trials regarding treatment effect was limited by the small sample size.

5.3.4 Examination of local infectious mononucleosis epidemiological data

5.3.4.1 Incidence rates

We determined the five-year average annual incidence rate for mono, in the Capital Health Region of Alberta, Canada, to be 1.11/1000 (95% CI (0.95–3.2)) for all ages and 5.46/1000 (95% CI (0.89–10.0)) for the 15-25 year old group.

5.3.4.2 Limitations

Calculation of accurate population based rates requires accurate data on the variable of interest (Monospot positive test results in this case) and on the population of interest. Limitations of our calculation include the post-hoc nature of the calculation, as well as the potential for the number of Monospot positive

cases to have been inflated due to the presence of either false positives or non-residents of our health region.

5.4 Conclusions

This doctoral work emerged from the knowledge that TCM is increasingly used by both adult and pediatric populations. It is also known that clinical research on TCM therapies is active in both populations (i.e. over 100 CCTs of TCM have been conducted in children) (Adams 2005), but syntheses of this knowledge are less common. Whether focused on safety or effect, rigorous literature summaries, including SRs, are essential to both practitioners and consumers in guiding informed practice and use. We have investigated the areas of TCM efficacy and safety research as well as barriers to research in our local environment.

We have demonstrated that although studies of TCM exist, methodological flaws often limit the meaningfulness and applicability of these studies, reinforcing the need for improved standards of conduct and reporting. We have also demonstrated that information on safety may lag well behind consumer use. TCM has a long history and provides unrestricted treatment options that are consumer driven. Thus, unlike some conventional medical treatments, proof of effect and safety through clinical studies are not a prerequisite for use. A comprehensive evaluation of risks of acupuncture in adults was only recently published (White 2004), and similar work in pediatrics has not yet been published. The only known review of pediatric acupuncture AEs was limited by numerous methodological choices (Jindal 2008). The SR of pediatric acupuncture AEs in this work provides the first comprehensive synthesis of this information, however, even so, we were limited by the paucity of primary data.

Through the conduct of an RCT, we attempted to add to the information on effect and safety of acupuncture therapy in adolescents and young adults with mono. Despite appropriate development, REB approval, and demonstration of methodological feasibility, we were unable to recruit sufficient patients to generate meaningful information on safety or effect. With respect to future

recruitment procedures for a similar population, based on our experiences, we would need to ensure buy in by enough clinics and health care centres to maximize our exposure to potentially eligible patients before beginning patient recruitment. This may involve assisting clinics in setting up methods to identify patients and notify recruiting physicians, that are effective and do not interfere with day-to-day clinic functioning. We also encourage University based health centres to consider participating more fully in research conducted on their campuses. In addition, we encourage health and research agencies to work together in developing methods of patient contact that balance the right to patient privacy and the right to participate in research that may benefit the individual or society.

5.5 Implications for Practice

5.5.1 Systematic reviews of TCM for mono and chronic fatigue

Convincing RCT evidence to support or refute the use of TCM for either mono or chronic fatigue was not identified. In the absence of high-level evidence, caution in application of TCM to these conditions is recommended.

5.5.2 Systematic review of acupuncture safety for pediatrics

Few serious AEs were identified but this may be due, in part, to under reporting and/or biased reporting. Mild AEs were determined to occur with a frequency of 7.8/100 patients (95% CI (6.3–9.2)) or 0.76/100 sessions (95% CI (0.61–0.90)) but this is based on a very limited number of RCTs and cohort studies. We join with other authors in calling for large prospective practice surveys to document the true incidence of AEs in practice, especially in children.

5.6 Implications for Research

5.6.1 Randomized controlled trials of traditional Chinese medicine

RCTs of TCM need to employ vastly improved methods in order for their results to be meaningful, especially those conducted in China. Reasons for the poor quality of Chinese RCTs include lack of understanding and training in research methods of authors (Wu 2009). Strategies to address these deficiencies in China, and elsewhere, include education and training initiatives as well as use of trial registries and publication guidelines (Boutron 2008, Fei 2008, Ioannidis 2004, Li 2009, Moher 2001, Zwarenstein 2008). Some of the specific aspects of clinical research that need to be urgently addressed include:

1. Use of appropriate study design for the question of interest (i.e. use of a CCT is likely to be less convincing than an RCT in efficacy research),

2. Use of methods appropriate to that study design (i.e. if the study is intended to be an RCT, allocation of patients needs to be carried out using an unbiased randomization technique);

3. Use of appropriate control or inclusion of multiple controls (i.e. comparison of two active controls, neither of which has been previously been shown to be effective, may be less meaningful than inclusion of a placebo or no treatment control);

4. Additionally, it has been recommended that the use of other forms of acupuncture as inactive controls, previously called 'sham or placebo' acupuncture, be discontinued as these techniques may in fact be 'active' treatments (Birch 2006, MacPherson 2008, Vickers 2002, White 2002, White 2006). Investigation into these effects is ongoing and experts in the field further recommend that studies that use or have used these techniques be relabeled to reflect the absence of a true placebo control;

5. Change in attitudes to negative results (i.e. negative answers to a research question may be just as valuable and informative as positive results and should be published). Given the tendency of some countries, including China, to only publish positive results, we wonder what information on our topics of

interest are missing from the published literature and thus unavailable for synthesis;

6. Similar recognition that reporting and publishing the absence of AEs is as valuable as reporting and publishing occurrence of AEs is required, in that full disclosure allows the determination of risk estimates based on more accurate numerator and denominator values.

5.6.2 Systematic reviews of traditional Chinese medicine

The quality of a SR is limited by the quality of included studies and adoption of the above recommendations is expected to reduce the number of SRs that state, "conclusions could not be drawn due to the poor quality of the included studies". Aside from the quality of review contents, the quality of SR methodology is an area that may be addressed separately.

1. As for RCTs, design parameters must be appropriate for the question (i.e. in a general safety review, it may not be sufficient to include only RCTs);

2. Given the global nature of clinical research and the limits on inclusion of foreign-language journals in standard databases, we encourage the use of foreign-language databases where possible, especially for research questions where much of the information is expected to be published in countries where English is not the primary language;

3. A vast amount of clinical research is generated in China every year, and it is unlikely that all the results are positive. Failure to report or publish negative effects or the occurrence of AEs is not of value in determining the true benefit or risk of an intervention, which is the goal of a SR;

4. Based on our experience, conduct of SRs of TCM therapies may be premature. Especially in cases where it is not possible to verify the methods of potentially relevant studies, it may be prudent to wait until initiatives to improve study quality have been shown to make a difference before including this material in a SR.

5.6.3 Barriers to clinical research

Our experience in conducting a pilot RCT highlights four main barriers to the conduct of clinical research: (i) absence of an accessible database of anonymous local health data that would enhance development of research studies; (ii) legislation meant to protect patient privacy, which severely restricts direct patient access; (iii) reluctance of physicians (who have direct access to patients) to participate in research; and (iv) reluctance of health care centres, including those on University campuses, to engage in research. Recommendations to counter these barriers and support or stimulate local health research include:

1. Providing ready access to anonymous local health data, for use by researchers in developing or conducting studies;

2. Partnership between health care and research agencies to establish methods of providing researches with access to health data and allowing patients, especially those who receive their health care from community practitioners, to be informed of new studies without violating privacy legislation; and

3. Encouragement by educational and licensing bodies, of physicians and health care centres, to actively participate in research, and implementation of measures that would make this participation feasible.

5.7 Reference List

Adams D, Cramer K, Vanderjogt L, Vohra S. Pediatric clinical trials of traditional Chinese medicine: A systematic review. *Journal of Complementary and Integrative Medicine.* 2005;2(1):Article 12.

Alberta Health and Wellness (AHW). *Health Information Act*. Edmonton, AB: Alberta Queen's Printers, 1999.

Barnes PM, Bloom B, Nahin RL. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. *National Health Statistics Reports*. 2008;12.

Birch S. A review and analysis of placebo treatments, placebo effects, and placebo controls in trials of medical procedures when sham is not inert. *Journal of Alternative and Complementary Medicine*. 2006;12(3):303-310.

Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Methods and processes of the CONSORT group: example of an extension for trials assessing nonpharmacologic treatments. *Annals of Internal Medicine.* 2008;148:6066.

Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERC), Social Sciences and Humanities Research Council of Canada (SSHRC). *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 1998* (with 2000, 2002, and 2005 amendments).

Egger M, Davey Smith G, Schneider M. Systematic reviews of observational studies In: *Systematic Reviews in Health Care: Meta-analysis in Context***,** M. Egger, G. Smith, and D. Altman Eds. London UK: BMJ Books, 2001 p211-213.

Fei YT, Liu JP. Improving the quality of reporting Chinese herbal medicine trials: an elaborated checklist. *Zhong Xi Yi Jie He Xue Bao.* 2008;6(3):233-238.

Fung I. Chinese journals: a guide for epidemiologists. *Emerging Themes in Epidemiology*. 2008;5:20.

Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher

D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine*. 2004;141(10):781-788.

Jindal V, Ge A, Mansky P. Safety and efficacy of acupuncture in children: a review of the evidence. *Journal of Pediatric Hematology/Oncology*. 2008;30(6):431-442.

Johannsen E, Schooley RT, Kaye K. Epstein-Barr virus (infectious mononucleosis), In Mandell, Douglas, and Bennett's *Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia, PA: Churchill Livingstone, 2005 p1801–1820.

Leung PC, Zhang L. Complications and adverse events in Chinese trials of acupuncture. *Acupuncture in Medicine*. 2008;26(2):121-122.

Li Y, Wu TX, Shang H, Yang K. Strategies for promoting the development of evidence based medicine in China. *Journal of Evidence-Based Medicine*. 2009;2(1):47-52.

LinYC, Bioteau AB, Ferrari LR, Berde CB. The use of herbs and complementary and alternative medicine in pediatric preoperative patients. *Journal of Clinical Anesthesia*. 2004;16(1):4-6.

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet.* 2001;357(9263):1191-1194.

Pilkington K, Boshnakova A, Clarke M, Richardson J. "No language restrictions" in database searches: what does this really mean? *Journal of Alternative and Complementary Medicine*. 2005;11(1):205-7.

Rea T, Russo J, Katon W, Ashley R, Buchwald D. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr Virus. *Journal of the American Board of Family Practice.* 2001;14:234-242.

Singer L, Karakis I, Ivri K, Gross M, Bolotin A, Gazala E. Characteristics of complementary and alternative medicine use by parents of asthmatic children in Southern Israel. *Acta Paediatrica*. 2007;96:1693-1697.

Spigelblatt L, Laine-Ammara G, Pless B, Guyver A. The use of alternative medicine by children. *Pediatrics*. 1994;94:811-814.

Tang J, Zhan S, Ernst E. Review of RCTs of TCM. *BMJ.* 1999;319:160-61.

Vickers A. Placebo controls in randomized trials of acupuncture. *Evaluation & The Health Professions.* 2002;25(4):421-435.

White A, Filshie J, Cummings T. Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complementary Therapies in Medicine.* 2002;9:237-245.

White P, Lewith G. Could neuroimaging help us to interpret the clinical effects of acupuncture? *Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschultz.* 2006;49:743-748.

WuT, Li Y, Bian Z, Liu G, Li J, Moher D. Randomized trials published in some Chinese journal: how many are randomized? *Trials.* 2009;10(46);doi:10.1186/1745-6215-10-46.

Xia J, Wright J, Adams C. Five large Chinese biomedical bibliographic databases: accessibility and coverage. *Health Information and Libraries Journal*. 2008;25:55-61.

Yamashita H, Tsukayama H, White A, Tanno Y, Sugishita C, Ernst E. Systematic review of adverse events following acupuncture: the Japanese literature. *Complementary Therapies in Medicine*. 2001;9:98-104.

Zwarenstein M, Treweek S, Gagnier J, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ*. 2008;337:a2390 doi:10.1136/bml.a2390.