Evaluation of the efficacy of a Chinese herbal medicine in the treatment of patients with osteoarthritis of the knee

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Abstract

Background

Osteoarthritis (OA) is common but has no outright cure. Current therapeutic drugs mainly treat OA symptoms and often cause undesirable side effects. Chinese medicine (CM) is a popular alternative therapy for OA, however the majority of CM efficacy studies have been methodologically inadequate. CM has traditionally treated OA under the clinical descriptor of 'Bi Syndrome' (painful obstruction syndrome) which includes a range of musculoskeletal disorders. An emerging theory treats OA as a combination of two types of CM Syndromes: Bi Syndrome and Wei Syndrome (atrophy syndrome). There is a lack of objective evidence with respect to possible CM Syndromes of OA, the reliability of CM diagnosis and efficacy of CM treatment guided by this emerging theory.

Objectives

To investigate the efficacy and safety of a Chinese herbal medicine (CHM) formula developed on the basis of this emerging theory in the treatment of symptoms of knee OA; to investigate the reliability of CM diagnosis in OA patients.

Methods

A double blind, randomised, placebo controlled clinical trial was conducted in eligible Australian OA patients. Participants were randomised to receive either CHM or placebo over 12 weeks, with a one month follow-up. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was the primary outcome variable. A CM examination conducted by two CM practitioners was incorporated. Data was analysed using SPSS software.

Results

There was no significant difference between the two groups in terms of change of the WOMAC indices of pain, stiffness and physical activity. However the stiffness index decreased significantly in the CHM group (only). Safety data indicated the CHM was safe and well tolerated. The new CM theory about treatment of OA as a combination of Syndromes was partially supported by the efficacy results. The reliability of CM diagnostic variables was generally low, and reliability was low for CM Syndrome

diagnosis according to Zang-fu Theory in patients with knee OA. Results support the notion that knee OA is an Interior, Deficiency and Yin disease.

Conclusion

There is some limited indication of a therapeutic effect for the CHM. Evidence in support of the emerging CM theory about OA is not conclusive. Larger scale studies over a longer time period are required.

Declaration of authenticity

I, Bin Hua, declare that the Ph.D thesis entitled ‘Evaluation of the efficacy of a Chinese herbal medicine in the treatment of patients with osteoarthritis of the knee’ is no more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

Signature Date

Acknowledgements

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Contents

Glossary of Chinese medicine

Acupuncture	A branch of Chinese medicine that is guided by the Theory of Meridians, a therapeutic technique involving the insertion of fine needles into the skin at specific points located along meridians
Auscultation	One of the four diagnostic methods, specifically listening to sounds
Ben	The root cause of a disease
Biao	Clinical manifestations of a disease
Bi Syndrome	A descriptor encompassing a collection of diseases mainly manifesting in pain, numbness, paralysis, lack of sensation and stiffness.
Blood	A collective term for nutrient and blood which nourish and moisten the whole body
Body fluids	A general term for all kinds of normal fluid in the body except Blood
Eight Guiding Principles	The guiding principles of Chinese medicine Syndrome differentiation include four pairs of principles: Yin and Yang, Exterior and Interior, Cold and Heat, Deficiency and Excess
Essence	The fundamenttal substance which is responsible for growth and development and maintain the body's vital activities
External causes	A collective term for the causes of a disease that originate outside of the body
Five Elements	An ancient Chinese philosophical system regarding the nature, interactions and relationships between five basic

	elements: wood, fire, earth, metal and water
Fu	A collective term for internal organs that perform certain physical functions of receiving and transporting, correspond with paired Zang organs
Heart	A functional organ system which governs Blood circulation and mental activities
Inquiry	One of the four diagnostic methods, case history taking by asking the patient a series of questions
Inspection	One of the four diagnostic methods, by observation of the body's shape, complexion, physique and mental state
Internal causes	A collective term for the causes of a disease due to emotions and mental activities or pathogenic factors within the body
Kidney	The organ system responsible for urination, storing vital Essence, promoting growth
Liver	The organ system responsible for storing Blood, and regulating the movement of Qi
Lung	The organ system responsible for controlling respiration, controlling Qi and regulating the 'water pathways' within the body
Meridians	A system of pathways through which Qi and Blood flow and connecting the internal organs within the body
Palpation	One of the four diagnostic methods, techniques involving touching and pressing the pulse or body parts to detect the disease
Qi	A form of life force, also, refers to the refined nutritive substance and functional activities of the body

Spirit	Refers to mental activities; also reflected in manifestations of the functioning of the body
Spleen	The organ system responsible for transporting and transforming food, distributing nourishment, and holds Blood within blood vessels and the internal organs in their correct place
Syndrome	A diagnostic conclusion of the pathological changes at a certain stage of a disease, which guides its treatment
Syndrome differentiation	The process of overall analysis of clinical data to achieve a diagnosis of a Syndrome
Wei Syndrome	A descriptor encompassing a series of progressive diseases caused by Qi and Blood and/or Body Fluid and/or Essence deficiency, manifesting as weakness of the sinews or muscles and/or loss of voluntary movement of the limbs
Yang	The male principle in Chinese philosophy with characteristics such as light, warmth, and dryness
Yin	The female principle in Chinese philosophy with passive characteristics such as inactiveness, darkness, and cold
Zang	A collective term for internal organs that perform major physical functions of storing and refining substances, functionally related to emotions, sense organs and tissues
Zang-Fu theory	A theory describing the physiological and pathological changes and functional relationships amongst the internal organs, mental activities, environmental factors and their external manifestations

Chapter 1 Introduction

1.1 Background of the research

1.1.1 Research into the clinical treatment of osteoarthritis of the knee with Chinese herbal medicine

Osteoarthritis (OA) is one of the most common forms of arthritis caused by 'wear and tear' on a joint, involving articular cartilage and subchondral bone. Research indicates that OA occurs more frequently with ageing, especially amongst the female elderly population.(Cicuttini et al., 1999, Ding et al., 2003, Jones et al., 2000, Crepaldi and Punzi, 2003) Body weight is also associated with development of OA. (Ding et al., 2005, Felson et al., 2004, Oliveria et al., 1999, Szoeke et al., 2006) In Australia, OA is the third largest contributor, especially among women, to life-years-lost due to disability, and the second leading reason for patient visits to a rheumatologist.(March and Bagga, 2004) The economic impact of OA on society is significant with respect to the resources allocated to treatment interventions, management of treatment side-effects, pharmacotherapy and surgery. Therefore, OA has recently become a considerable problem for ageing and obese populations, as is prevalent in Australia.(Australian Bureau of Statistics, 2010, Department of Health and Ageing, 2009, Felson et al., 2000)

In most cases, OA is characterised by symptoms of pain and stiffness. There is no outright cure for OA yet, although a variety of treatments can help people control symptoms and reduce the effects of the disease. Treatment generally involves a combination of exercise, lifestyle modification, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), arthroscopic interventions or joint replacement surgery.(Hunter and Lo, 2009) However, the most widely prescribed western medications, such as NSAIDs and Cyclooxygenase-2 (COX2) inhibitors, are associated with serious side effects, including bleeding and perforating ulcers, and increase the risk of cardiovascular disease, such as myocardial infarction.(Hippisley-Cox and Coupland, 2005, Hudson et al., 2005, Juni et al., 2005)

Hence, people are looking for different therapies, with good efficacy and low toxicity, in the treatment of OA, and are turning increasingly to complementary and alternative medicine (CAM).(Long et al., 2001) An Australian study found that as many as 40%

of OA sufferers used CAM.(Zochling et al., 2004) Furthermore, a study by MacLennan and colleagues showed a high use of CAM products and therapies in Australia for chronic illnesses, like OA, and a significant increase in the number of women using herbal medicine since 2000.(MacLennan and Wilson, 1996, MacLennan et al., 2002, MacLennan et al., 2006)

Chinese medicine (CM) has been practised as mainstream medical care for thousands of years in China. As one of the major forms of traditional medicine in the world, CM is gradually becoming accepted as an alternative medical system in many western countries.(WHO, 2005) CM includes Chinese herbal medicine (CHM), acupuncture and moxibustion and other therapies such as Qi Gong and Tai Chi (exercise therapy), diet therapy and massage. CHM is a popular modality of CAM. The predominant reason for patients trying herbal medicines is the desire to benefit without incurring the risk of adverse effects.(Weiner and Ernst, 2004) CHM and acupuncture have been widely used for treatment of OA of the knee and chronic knee pain in China. However, there are few rigorous studies of the efficacy and safety of CHM in the treatment of OA to date. While some clinical studies have suggested that CHM may be effective in the treatment of OA symptoms, many were not randomised nor were they 'placebo controlled'.

The term 'osteoarthritis' did not exist in ancient Chinese medical books, but many descriptions of diseases in those books were very similar to the clinical and pathogenic characteristics of OA. In CM it is generally thought that OA should be categorised as 'Bi Syndrome', and more specifically 'Bi Syndrome of Bone'. The word 'Bi' means painful obstruction which causes such symptoms as pain, numbness, paralysis, lack of sensation and stiffness. Bi Syndrome can refer to a range of rheumatologic diseases which demonstrate those symptoms mentioned above, such as rheumatoid arthritis, sciatic neuritis, osteoporosis, and gouty arthritis. Thus, the term Bi Syndrome is not a one-to-one correlation with OA. Although OA and degenerative arthritis are both classified as 'Bi Syndrome of Bone' by the official clinical guidelines of the People's Republic of China,(China State Administration of Traditional Chinese Medicine, 1994, China State Bureau of Technical Supervision, 1997), there is a lack of empirical data and rigorous research to support this classification. There have been arguments as to the classification of OA by CM practitioners over the past few decades. A new theory which considers OA as a

combined pattern of Bi Syndrome and 'Wei (Atony) Syndrome' has been applied in clinical practice relatively recently, with the fundamental disorder understood as being Wei Syndrome and the secondary disorder being Bi Syndrome. Wei Syndrome is characterised by weakness of the muscles and sinews (explained in more detail in Chapter 5). Clinical anecdotal evidence in a major hospital in China supports this combination theory and the effectiveness of CHMs developed according to this theory in treating OA. Two clinical trials demonstrated that a CHM formula, which was designed based on this combination theory, achieved better clinical effectiveness than Ibuprofen and Viartril-s (a chondro-protective drug).(Shi et al., 1994, Cao et al., 2005) In addition, there have also been some animal studies that found the same formula could improve the cartilage quality of OA mice at the histopathological level.(Wang et al., 1998, Shen et al., 1995) Given the encouraging but limited scientific evidence available in support of this emerging theory, one of the main purposes of this thesis was to investigate this emerging theory in a scientifically rigorous manner. Therefore, a CHM formula was developed in accordance with this new theory, based on the original CHM investigated in previous clinical trials. The efficacy and safety of this CHM was then tested in a randomised, double-blind, placebo-controlled pilot study in patients with OA of the knee.

1.1.2 Research into the reliability of Chinese medicine

CM differs from conventional medicine (western medicine) in a number of ways. In general, the CM diagnostic approach relies more on the clinician's interpretation of the patient's symptoms and signs rather than on laboratory tests, tending to be far more conceptual and less technologically driven.(Zhang et al., 2003) The concept of 'disease' in CM is different from that in western medicine. In CM the term 'disease' may correspond with a biomedically-defined disease or condition, a disorder, or even just a symptom or a sign. For example, abdominal pain is a disease name in CM, referring to a disease category for those medical conditions in which abdominal pain is the chief complaint, but it is just a symptom in western medicine. In CM, Syndrome Differentiation is the ultimate goal of the diagnostic process. The CM 'Syndrome' or underlying 'pattern of disharmony' is a subcategory of a disease/disorder, and is the summary of the overall picture of disharmony formed by the current symptoms and signs. The CM Syndrome diagnosis indicates the aetiology and pathogenesis of the condition, and the relevant treatment for the disharmony. In CM, a disease/disorder

may have several different types of CM Syndromes in some cases representing different stages of development of a disease. There may be more than one CM Syndrome present at one time also. In CM, the Syndrome has been treated as the pivotal part of diagnosis, since treatment is aimed at the disease and its CM Syndrome. The process of CM diagnosis starts with the collection of clinical data, by taking a case history and making an overall observation clinical signs, analysis of these according to CM theories (data analysis) and then drawing a conclusion with regard to the disease and CM Syndrome (data summary).(Deng et al., 1984, Maciocia, 2004)

The investigation of the reliability of CM diagnosis is a relatively new field. A few studies have been conducted into the reliability of the CM diagnosis in a small number of diseases and conditions, mostly according to Zang Fu Theory, one of the main theories of CM.(Zhang et al., 2004b, Sung et al., 2004, MacPherson et al., 2004, Hogeboom et al., 2001, Birch and Sherman, 1999, Coeytaux et al., 2006, Zhang et al., 2005a, O'Brien et al., 2009a) There was only one study (O'Brien et al., 2009b) which has comprehensively examined the reliability of three out of the four main methods of collecting clinical information (Inquiry, Inspection, Auscultation and Palpation). There have been no studies that have investigated the reliability of all four diagnostic methods in CM in a CM examination. In addition, there is still a gap in knowledge of the reliability of CM Syndrome diagnosis according to one of the fundamental theories used to analyse data, the ‘Eight Guiding Guiding Principles’. Although there were some efforts to investigate the reliability of CM Syndrome diagnosis in rheumatoid arthritis, (Zhang et al., 2004b, Zhang et al., 2005a, Zhang et al., 2008a) there have not yet been any studies in OA. It is important to investigate the reliability of diagnosis with respect to patients with OA, so that more reliable treatments for this disease can be applied. If diagnosis is unreliable, and as CM treatment is dependent on the Syndrome diagnosis, this could lead to treatment being unreliable and therefore there could be less confidence in treatment.

In addition, CM practitioners usually use those diagnostic variables as evidence of change in clinical practice. If CM diagnostic variables are consistent, then these could be used in clinical trials as outcome indicators to assess the efficacy of CM therapies in addition to western medicine tools. Thus, it is important to test the reliability of these CM diagnostic methods first.

Finally, there is no empirical data about the CM Syndromes of OA. The literature provides many ideas about what CM Syndromes exist, although a lot of literature relates it to Bi Syndrome.

Therefore, in this research project, a sub-study of the reliability of the CM diagnostic process was conducted as part of a clinical trial investigating the efficacy of a CHM in the treatment of knee OA

1.2 Study process

The research conducted was a pilot study intended to obtain information about the effectiveness and tolerability of the administration of a CHM that was formulated according to an emerging CM theory about the treatment of OA. This theory proposes that OA should be considered as a combination of Wei Syndrome and Bi Syndrome, with Wei Syndrome predominant. The study design was a randomised, double-blind, placebo-controlled parallel group study to examine the efficacy of a CHM formula, the Bai Niu Capsule (composed of six Chinese herbs in common usage in Australia and China), in alleviating symptoms of OA of the knee. The study was conducted over 12 weeks with a 4 week follow-up period. The primary outcome measures were the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Short Form Health Survey (SF-36). The additional measures for the efficacy of the herbal medicine were the Patient Global Assessment and the Physician Global Assessment. The study also collected data concerning the safety and tolerance of the Chinese herbal medicine, including biochemical and metabolic tests, vital signs such as blood pressure and heart rate, and assessment of any side effects and/or adverse events.

An inter-rater reliability sub-study of the clinical trial was conducted between two Chinese medicine practitioners in order to test the consistency of the CM diagnostic process. The sub-study was designed to assess the reliability of clinical data (signs and symptoms) collected using the four diagnostic methods of Chinese medicine diagnosis: inquiry, inspection, auscultation and palpation. The sub-study also assessed the reproducibility of CM Syndrome diagnosis using two major theories of Chinese medicine, the ‘Eight Guiding Principles’and ‘Zang-Fu Theory’.

1.3 Contribution of research to knowledge

Firstly, this study is the first clinical trial conducted in Australia according to strict scientific protocol to investigate the efficacy of a CHM formula in alleviating symptoms of OA of the knee. Although NSAIDs and acetaminophen have been widely used in the treatment for OA, there are still many patients who are unresponsive to western pharmacologic drugs, or unable to tolerate the side effects of such medications. The use of various forms of CAM has become more popular recently, with the benefit a reduced the cost burden of OA.(Segal et al., 2004, Zochling et al., 2004) It is important that alternatives like CHM are subjected to rigorous scientific scrutiny to establish that these are genuine, safe and efficacious medicines. The majority of studies of the efficacy of CHM treatment of OA of the knee have suffered from methodological short-fallings. Thus, the current research is a contribution to the field of CM, applying rigorous scientific methodology to a clinical study of CHM in patients with OA. In addition the study CHM formula designed for this trial was based on a relatively new theory that OA should be treated as a combination of Wei Syndrome and Bi Syndrome, with Wei Syndrome predominant. This research is an original contribution to CM knowledge, investigating the efficacy and safety of a novel CHM designed on the basis of this new theory, and attempting to provide empirical evidence for or against this new theory.

Secondly, this project has also included a sub-study that comprehensively investigated the consistency of the CM diagnostic process from the initial stages of data collection using all four diagnostic methods, something that no other study has previously done, through to data analysis according to two main theories that are commonly used to arrive at a CM Syndrome diagnosis. Only one other study (O'Brien et al., 2009b) has assessed the CM diagnostic process using three of the four diagnostic methods, so this study is contributing important data with respect to reliability of data collection. This study also investigated the reliability of the Eight Guiding Principles and Syndrome diagnosis according to Zang-Fu Theory, which is a contribution to a small but growing body of knowledge with respect to reliability of CM Syndrome diagnosis. Furthermore, no study has assessed the reliability of CM diagnosis in OA patients. Thus, this study is contributing novel information about the possible CM Syndromes of knee OA.

Thirdly, this study represents an integrated approach to study design of CM by integrating biomedical endpoints and CM variables into the assessment process as part of the study methodology. This is an example of a cross-disciplinary clinical research design to explore the application of the evidence-based medicine approach in CAM. This project offers a way forward for scientific research into CHMs which have not been widely studied widely at the clinical level in western countries.

1.4 Thesis structure

This thesis consists of three sections.

Section 1 (Chapters 1-6) provides the background of the thesis, addressing the current knowledge about OA of the knee and its treatments from the perspectives of biomedicine and CM Since this thesis is written for an audience not trained in CM, a background chapter on CM theory is provided. A summary of the current knowledge about inter-rater reliability in CM is included.

Section 2 (Chapters 7-8) explains the methodology of this clinical trial and an analysis of the CHM formula used in the study and the individual herbal constituents, from the western medicine and CM perspectives.

Section 3 (Chapters 9-12) reports the results of the clinical trial and the inter-rater reliability sub-study, draws conclusions and discusses potential ways forward in the research of CHM.

Chapter 2 An Overview of Chinese Medicine

2.1 Introduction

Chinese medicine (CM) is one of world's major forms of traditional medicine and has been practised for thousands of years. CM originated in ancient China several thousands of years ago. It is still well-accepted as mainstream medical care in modern China and is also popular as a healthcare system amongst many people in China's neighbouring countries and areas.(WHO, 2005) It is considered an alternative medical system in western countries.

The modalities of CM includes herbal medicine, acupuncture and moxibustion and other non-medication therapies associated with CM such as qi gong and tai chi (exercise therapy), diet therapy and tuina (massage). It is characterised by holism and the treating of diseases according to 'Syndrome Differentiation', and is guided by several key theories. (WHO, 2007, Committee for Terms in TCM, 2005)

Holism is the foundation of CM, regarding the human body as an organic whole (biological, mental and social), which is integrated with the external environment. Disease is understood to occur as a result of physical, emotional, spiritual, social and environmental imbalance. Accoring to CM theory, five *Zang* Internal Organs are the central in the human body. These are associated with six *Fu* Internal Organs, and connected with corresponding sense organs, tissues and skin to form an organic body through the Meridians. The Meridians refer to a network in which vital substances of the body circulate, connecting the internal organs, extremities, sense organs and tissues, making the body an organic whole.(WHO, 2007) The functioning of body relies on this systematic connection and the interaction of certain vital substances, such as 'Qi' and 'blood' (explained later). In addition, the human being is living in nature. Any change in the natural environment will affect the human body directly or indirectly because human are in adaptive relationship with the natural environment. If the change of the natural environment goes beyond the body's physiological function, and ability to adapt to change, then pathological reaction will occur leading to diseases.

Syndrome differentiation is another central tenet of CM. In allopathic medicine, a 'syndrome' refers to the combination of several clinical features, signs, symptoms and

phenomena that often occur together. However, a 'CM Syndrome', also known as 'pattern of disharmony', is a subcategorisation of a disease or disorder or symptom which is characterised by a collection of signs and symptoms indicative of the state of body and underlying pathogenesis at that point in time, as understood according to CM theory. A disease/disorder typically has three to six CM Syndromes. Each CM Syndrome may be treated by different herbs or acupoints, that is, treatment is not only aimed at the disease, but at the CM syndrome. A patient may have a combination of CM Syndromes at one point in time, but usually one of them is predominant. Syndrome Differentiation is the process of overall analysis of clinical data (signs and symptoms) to determine the location, cause and nature of a patient's disease and to make a diagnosis of a CM Syndrome.(WHO, 2007)

Unlike allopathic medicine, CM is not reductionist in approach. CM does not rely on medical technology and the quantification of measurements of diagnostic variables (for example, at the tissue or cell or gene level) to understand the state of the human body. CM considers external signs and subjective sypmtoms in their entirety and summarises them in terms of a disease/disorder and a CM Syndrome. Diagnosis and treatment aim at the whole body rather than focussing just on individual symptoms or signs. Treatment focuses on the root cause of illness (termed the 'ben') and the symptoms (the 'branch' or in Chinese, 'biao'). Although CM is characterised by diversity in clinical practices, the theoretical foundations of CM were formed thousands of years ago and have been passed down through generations. In this chapter, the basic concepts and theories of CM will be explained. In addition, the CM understanding of aetiology and pathogenesis of disease and the diagnostic system will be discussed, and the concept of Syndrome Differentiation expanded on. Lastly, the theoretical foundation of Chinese herbal medicine will be explained.

2.2 Chinese medicine concepts and theories

2.2.1 Yin-Yang Theory

Yin and Yang can be considered simple and at the same time very profound concepts in CM. Yin Yang Theory is the fundamental theory of CM which distinguishes CM from other traditional medicines.(Maciocia, 2005) Yin and Yang are two philosophical terms representing opposite but complementary qualities, used in ancient China to explain how things in the world work. Yin and Yang represent two

states in the process of change and transformation of all things. They can also be described in terms of energetic forces. In ancient times peasants watched the changing light and shadow on the side of a mountain as the sun passed overhead. Yin was used to indicate the shady side whilst Yang indicated the sunny side.(Maciocia, 2005) The Yin Yang Theory grew out of this and analogies with other phenomena in nature were drawn: Yin was associated with cold and night, Yang with heat and day. Yin would be associated with dark, passive, downward, cold, contracting and weak, while Yang would be associated with bright, active, upward, hot, expanding, and strong. Eventually it was applied to the human body.

However, Yin and Yang are also interconnected and interdependent, and give rise to each other in turn. These two energies interact with each other, and Yin may transform into Yang and Yang into Yin, causing all manner of phenomena, for example temperature changes from hot to cold, and the processes of expansion and contraction. There are four aspects of Yin-Yang relationship: the opposition of Yin and Yang; the interdependence of Yin and Yang; the mutual consuming of Yin and Yang; and the inter-transformation of Yin and Yang.(Maciocia, 2005) Although everything contains Yin and Yang, these are always in a dynamic balance (rather than in a constant 50:50 proportion). These opposite characteristics are interdependent, that is one cannot exist without the other, like brightness cannot be observed if there is no darkness. When either Yin or Yang is out of balance, their proportion will be changed to achieve a new balance. This aspect has significant implications in CM and is termed ‘Yin-Yang mutual consumption’. When Yin is weak, Yang becomes seemingly ‘excessive’ (in relative excess), and when Yin is predomiant, Yang can be decreased due to the excess Yin consuming Yang. For this reason, it is important to differentiate which is primary and which is secondary. In the case of an ‘absolute excess Yin’, this is primary, and as a consequence, Yang is relatively weak (the excess of Yin consumes Yang). However, in the case of weakness of Yang, this is primary, and as a consequence, Yin is in apparent excess (Yin does not consume Yang in this case). This has consequences for how illness is treated in CM. Although Yin and Yang can transform into each other, this change is based on the presence of certain internal conditions when the conditions are ripe. Therefore, in CM, every treatment can be categorised into four strategies: tonify Yang, or tonify Yin, or eliminate excess Yang, or eliminate excess Yin.(Maciocia, 2005)

In CM, anything can be explained or analysed by Yin-Yang theory, such as categorising body parts, explaining physiological functioning of the body and pathological changes in the body, and guiding diagnosis and treatment. For example, in applying it to categorising the body parts, the back is Yang and the front is Yin; the interior of the body is Yin and the exterior part is Yang. In terms of applying it to pathogenesis, a rapid onset diesase is considered Yang and a disease with gradual onset is Yin.

It is important to note that the balance of Yin and Yang is always in a dynamic change, even when the body is healthy. For example, during times of anger, a person's mood is fiery (Yang), and yet once the person has been calmed down, and a quiet peaceful state (Yin) is achieved. This shift in the balance of Yin and Yang is very natural. But if the balance of Yin-Yang has been altered, and one (Yin or Yang) dominates the other, health may become compromised, resulting in illness and disease. CM practitioners attempt to determine the exact nature of the imbalance, and then correct it through the use of acupuncture, herbal remedies, exercise, diet and lifestyle. As balance is restored in the body, so is health.

2.2.2 Five Element Theory

Five Element Theory is a philosophical system used for describing interactions and relationships between phenomena. This theory along with Yin-Yang Theory form the theoretical foundation of CM and serve to make CM distinctively different from western medicine.(Maciocia, 2005) The Five Elements, five basic elements of the material world are Metal, Wood, Water, Fire and Earth. These elements are in constant movement and change. By way of analogy to the elements and their associated characteristics, the ancient Chinese attributed different phenomena to the categories of the five elements. A system of correspondences between the elements, seasons, directions, colours, tastes, internal organs, sense organs and other attributes was developed. These are set out in Table 2.1 and Table 2.2.(Ni, 1995)

Table 2.1 Main correspondence between natural phenomena and the Five Elements

	Wood	Fire	Earth	Metal	Water
Basic Qualities	Can be bent and straightened	Flares upwards	Permits growing and harvesting	Can be moulded and hardened	Moistens downwards
Movements	Expansion	Upwards	Keeping in the centre	Contraction	Downwards
Directions	East	South	Centre	West	North
Seasons	Spring	Summer	Late summer	Autumn	Winter
Climates	Wind	Heat	Damp	Dryness	Cold
Colour	Green	Red	Yellow	White	Black
Farming	Birth	Growth	Transformation	Harvest	Storage

Table 2.2 Main correspondence between human body and the Five Elements

	Wood	Fire	Earth	Metal	Water
Yin Organs	Liver	Heart	Spleen	Lung	Kidney
Yang Organs	Gall Bladder	Small Intestine	Stomach	Large Intestine	Urinary Bladder
Sense Organs	Eye	Tongue	Lip	Nose	Ear
Tissues	Tendon	Vessel	Muscle	Skin	Bone
Body Fluids	Tear	Sweat	Saliva	Mucus	Urine
Emotions	Anger	Joy	Distress	Sadness	Fear
Tastes	Sour	Bitter	Sweet	Pungent	Salty

The interactions or interrelationships between the Five Elements are described by two cycles, a generating or creation cycle, also known as "mother-son" (xiang sheng) cycle, and a controlling or overcoming or destruction (xiang ke) cycle. The generating cycle refers to: Wood feeds Fire; Fire creates Earth; Earth bears Metal; Metal smelts into Water; Water nourishes Wood and is depicted by the arrows

creating the circumference of the circle in Figure 2.1. The overcoming or controlling cycle relationships are: Wood parts Earth (such as roots penetrate into Earth); Earth absorbs Water; Water extinguishes Fire; Fire melts Metal; and Metal chops Wood. These relationships are depicted by the arrows and the circle in Figure 2.1

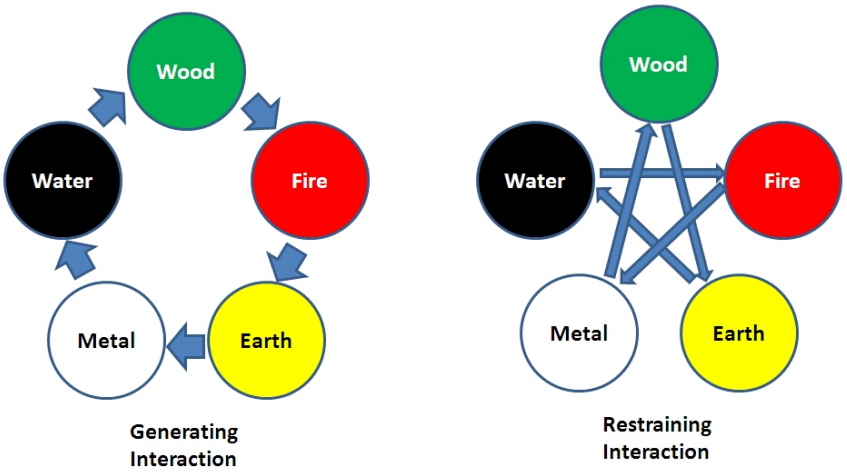

Fig2.1 The interactions of the Five Elements

Five Element theory may be applied in understanding physiology and pathology, guiding diagnosis and treatment. It is also applied in the understanding of herbal medicine. For exampleeach herb has a certain taste that is related to one of the Elements, and each taste is related to a therapeutic action. Knowledge of Five Element theory can be used to choose herbs in a medicinal formula. For example, the sour taste (Wood) herbs can generate fluids and control perspiration (Fire), because Wood feeds Fire.

2.2.3 The Vital Substances

In Chinese philosophy and medicine, the vital substances of the human body which maintain life and functional activities refer to both material and non-material phenomena. These include Qi, Blood, Essence (Jing), Body Fluids and Spirit (Shen).(Ni, 1995)

Qi is frequently translated as ‘energy’ and is considered a vital force responsible for controlling the workings of the human mind and body. But this only partially represents its manifestations. The concept of Qi is based on the ancient Chinese initial understanding of natural phenomena. Qi is the most basic substance of which the world is comprised. Everything in the universe results from the movements and

changes of Qi. That is, we live in a universe in which everything is interconnected, and a human being's Qi is a result of the interaction of the Qi between Heaven and Earth. What happens to one part of the body affects every other part of the body. The mind and body are not viewed separately, but as part of an energetic system as well. Therefore, Qi has two properties: invisibility and motion.

In CM, Qi is believed the most fundamental substance in the construction of the human body and in the maintenance of its life activities. Generally speaking, Qi of the human body has five functions: generating, warming, defending, controlling and transforming.(Yin and Zhang, 1984) 'Generating' means Qi promoting the growth of the body, the circulation of Blood, and waste excretion. Warming refers to Qi maintaining the temperature of the body. 'Defending' means Qi expels external pathogenic factors. 'Controlling' means that Qi keeps the organs in their own locations and prevents Blood and Body Fluids from extravasating. 'Transforming' refers to the role of Qi in body metabolism and in transformation of the forms of vital substances. Qi is a material concept and a functional concept. In a material sense Qi refers to the refined energy produced by the Internal Organs which nourishes the body and mind. In a functional sense, Qi simply indicates the functional activity of the internal organs, and is referred to in relation to particular internal organs e.g. Liver Qi, Heart Qi and Stomach Qi.(Maciocia, 2005)

The concept of Blood in CM is a mixture of visible and invisible substances. It includes blood as understood in biomedicine, however from another perspective it is more akin to another form of Qi. First of all, in CM it is understood that Blood is generated from food by the 'nutrient Qi' (generated by the 'Spleen' organ), aided by 'Original Qi' (the fundamental Qi of human body related to Essence). Secondly, the motive force for Blood circulation is Qi. Thirdly, the holding function of Qi ensures that Blood circulates in the vessels without extravasating. Therefore, Blood can be regarded as a very dense form of Qi. Blood has some unique functions such as nourishing the body, moistening the body and 'housing the Mind' or 'Shen' (akin to consciousness). In addition, Blood also nourishes Qi, so there is a very close relationship between Qi and Blood. For example, in some cases, the patient will develop signs of Qi deficiency (the level of Qi of the body has been decreased) after a loss of blood, such as sweating and cold limbs.

Body Fluids are liquids inside the body that have originated from food and drink. In a narrow sense, it could be equated to body fluids in biomedicine. However, Body Fluids in CM include an invisible substance that circulates with Qi, which can be separated into a pure or impure part. The pure part goes upwards to moisten the tissues and organs and the impure part is excreted from the body. If there is a dysfunction of transformation, transportation and excretion of the Body Fluids, the result may be 'dryness' or accumulation of 'dampness' (explained in Section 3.1).

Essence (Jing) is a kind of refined substance transferred from the parents to the child, akin to genetic material in an energetic sense. Jing is supplemented by Qi generated through eating and drinking ('nutrient Qi'). Essence provides the material basis to produce Qi and life, forming the basis for growth, reproduction and development and ageing. Shen or Spirit is a non-material type of Qi which has broad links to all kinds of body functions, sense and emotions. CM emphases the integration of body and mind, so Essence (Jing), Qi and Spirit (Shen) have always been highlighted in CM theory.

2.2.4 The Internal Organs: Zang-Fu Theory

In CM the Internal Organs, termed Zang Fu, are not simply anatomical organs, but may be thought of as functional systemsinvolved in the physiological functioning of the body. The Theory of Zang Fu organs, Zang-Fu Theory is a core CM theory, linking body functions, emotions, mental activities, tissues, sense organs and environmental influences. There are two categories of Internal Organs in CM: Yin organs (Zang) are the solid organs, and Yang organs (Fu) are the hollow organs.

Yin organs store pure and refined vital substances like Qi, Blood, Body Fluids and Essence taken from the hollow Yang organs after transformation from food. In contrast to Yin organs, Yang organs are constantly filled and emptied to carry out the process of transformation, extracting the pure essences and excreting the waste products. Yin organs are the Heart, Liver, Spleen, Lung, Kidney and Pericardium, whilst Yang organs refer to the Small Intestine, Large Intestine, Gall Bladder, Urinary Bladder, Stomach and Triple Energiser.(Ni, 1995)

The functions of the Zang-Fu Organs are considered to be vital. Each organ has multiple functions. In brief, the Lung governs respiration, the extraction of Qi from

the air, and plays a role in fluid metabolism. The Spleen governs the transportation and transformation of nutrients, forming ‘nutrient Qi’ that circulates to nourish all parts of the body. The Heart governs the circulation of Blood and is the residence of ‘Shen’ (Spirit or consciousness). The Kidney is mainly responsible for fluid metabolism and the storage of Jing. The Liver ‘stores the Blood’ and is responsible for maintaining the free flow of Qi throughout the body. The Pericardium (not always considered a Zang Organ) protects the Heart.

The Yang Organs and their functions are described as following. The Stomach is responsible for initiating the metabolism of food and drink. The Large Intestine and Urinary Bladder are responsible for excretion of faeces and urine respectively. The Gall Bladder governs the storage and secretion of bile. The Small Intestine and Triple Energiser (which has no corresponding physical Zang organ) assists the process of water metabolism and fluid flow.

The Yin (Zang) and Yang (Fu) organs play critical roles in the interrelated network of the body, mind and spirit. Each organ has a corresponding organ that it is responsible for either negatively or positively regulating. The manner in which the organs interact with each other is described by the Five Element Theory, described previously. The interrelationship between the Zang and Fu and their related sense organs is set out in Table 2.2. Howeverfor the Pericardium and Triple Energiser do not share a close relationship according to the traditional view.

CM diagnoses rely on the identification of underlying patterns of dysfunction in the patient as understood according to the Five Element Theory, Yin-Yang Theory and in particular, Zang-Fu Theory. A thorough understanding of each organ's function and symptoms of dysfunction will give an insight into the process of disease and illness, and guide treatment.

2.2.5 The Meridians

The Meridians, often called ‘channels’, refer to a network in which Qi and Blood circulate, connecting the internal organs, extremities, sense organs and tissues (skin, muscle and tendon), making the body an organic whole.(WHO, 2007) The Theory of Meridians is an important component of the theoretical system of CM. It covers the physiological functioning and pathological changes of the Meridians and ‘Collaterals’

(the small branches of the meridians, serving as a network linking the Meridians, the main network, and the various aspects of the body), and their inter-relations with the Zang Fu organs. This theory is utilised in guiding clinical practice, especially acupuncture treatment.

There are twelve main Meridians in the body along the arms and the legs, six Yin and six Yang. Each relates to and is named after one of the Zang-Fu organs, passing through its same-named organ. Meridians linked with Yin organs are known as Yin Meridians; if they are linked to Yang organs, they are called as Yang Meridians. Apart from these twelve principal Meridians, there are eight extra Meridians, a smaller Meridian network ('Collaterals'), which are regarded as storage vessels or reservoirs of energy (Qi) and are not associated directly with the Zang-Fu organs. Amongst the eight extra Meridians, the Governor Vessel and the Conception Vessel are considered the most important channels, because they contain acupuncture points which are independent of the twelve principal Meridians. The flow of Qi in the Meridian system concentrates in certain areas of the skin. These areas are very small points known as 'acupoints'. Although acupoints are located externally and superficially, they can affect the internal functions of the body. There are 365 acupuncture points, and each point belongs to a particular Meridian channel that connects to specific organs.

In CM, patterns of physiological and emotional disharmony are thought to be caused by blockages or disruptions of energy flow along the Meridians. When pathogenic factors invade the skin and the pores are open they enter the Collaterals and move into the Meridians, or may even transmit to and reside in the Zang-Fu organs. Needling, moxibustion or (simply) the application of pressure can be applied on the Meridians to correct such dysfunctions. Acupoint selection and prescription combinations are all made on this basis. In clinical practice, the sensation generated through the Meridians by stimulating an acupoint, felt by the practitioner and by the patient, is believed to be crucial. This sensation is called 'De Qi' or 'the arrival of Qi'. It is believed that without this sensation it is hard to achieve a therapeutic effect. In addition, the way in which Chinese herbs are understood to work is based on the relationship between the Meridians and the Zang Fu organs.

Although the Meridians work as a channel system which carries and distributes Qi and Blood, they are not blood vessels or nerves. Many Meridian research projects have been carried out to test different hypotheses of how this system works. Although the existence of the Meridian phenomena has been confirmed, researchers have not found out any specific biological model that can give a complete anatomical description of the Meridian system.(Wang et al., 2010)

2.3 Aetiology and pathogenesis

2.3.1 Aetiology

In general, aetiology refers to the causes of diseases or pathologies, or even the reasons behind the way that things act. The ancient Chinese realised that there are many factors which may bring about imbalances in the human body and thus disease, such as climate abnormalities, pestilence, emotional stimulation or disturbances, injury, irregular diet, and insect bites. Others include pathological products of diseases such as blood stasis, and phlegm. All of these contribute to imbalances within the human system which has an intimate relationship with the environment. When this dynamic balance has been disturbed, for any reason, and the body is unable to restore it spontaneously, illness can result. The factors that lead to such disharmony are the causes of illnesses. There are internal, external and non-internal/external causes in CM aetiology. However, it should be noted that the occurrence of a disease in particular depends on the state of the body's resistance. The development, transformation and prognosis of a disease depend on the balance of body's Defensive Qi (that form of Qi that defends the body from attack from pathogenic factors) and the pathogenic factors.

2.3.1.1 External causes of disease

The external causes of disease refer to climatic factors, which are Wind, Cold, Summer-Heat, Dampness, Dryness and Fire. CM holds that an exterior pathogenic factor invades the body when there is a temporary imbalance between a climatic factor and body's Qi at that particular time. The human body has the ability to adapt to climatic variations. However, when the body's Qi is too weak to adapt to climatic changes or if there is an abnormal change of the weather which surpasses the normal

body's Defensive Qi, then the six climatic factors can become pathogenic factors and bring about the occurrence of disease.

Each of those six external causes is associated with a certain season and also can be categorised into a Yin or Yang pathogen (see Table 2.3). Any of the climatic pathogenic factors can actually occur in any season except for Summer-Heat. The association of the pathogenic factors with a particular season is simply indicative of the characteristics of the external cause. In addition, if diseases have symptoms similar to the Syndromes caused by external factors, but are the result of dysfunction of the Internal Zang-Fu organs, their causes are usually identified as Internal Heat, Internal Damp, Internal Dryness, and Internal Fire.

Table 2.3 Characteristics of External Factors

External Factors	Characteristics	Associated Season	Yin-Yang Category
Wind	Rapid movement; swift change; ascending and opening actions	Spring	Yang
Cold	Deceleration of activity; coagulating and contracting actions; damage Yang Qi	Winter	Yin
Summer-Heat	Hotness; evaporation (consuming Qi, Yin and Body Fluids)	Summer	Yang
Dampness	Heaviness; stickiness; downward flowing; obstructing Qi movement	Late Summer	Yin
Dryness	Lack of moisture; consuming Yin and Body Fluids, tend to injure Lung	Autumn	Yang
Fire	Intense heat; upward flaring; damaging Yin with a tendency to induce bleeding; disturbing the mental activities	Summer	Yang

In addition, the external factors can also attack the body together, for example Wind-Heat, Wind-Cold, Wind-Dryness, and Cold-Dampness. Therefore, the diagnosis of an invasion of an exterior pathogenic factor should be made from the analysis of clinical manifestations (the pattern of disharmony), rather than simply finding out if the patient has been exposed to a particular climatic factor.

2.3.1.2 Internal causes of disease

The internal causes of disease are emotions and mental activities which injure the Internal Organs directly, causing disease. Emotions are an integral and inseparable part of the actions of the Internal Organs. Under normal conditions the emotions will not cause disease. However, if the emotions are too stressful and constant, or the patient is too sensitive to stimulation, then emotions may induce acute or long-standing changes which result in diseases, and become pathogenic emotional factors. There are seven internal-emotional causes of disease: Anger, Joy, Sorrow, Anxiety, Thought, Fear and Fright.

In CM, each emotion corresponds to a relevant Internal Organ. Each organ produces a certain mental energy for that emotion. Therefore, there is an interaction of body and mind.(Maciocia, 2005) The relationships between the emotions and the Internal Organs are set out in Table 2.4. It is important to note that each emotional stress affects the circulation of Qi and the Heart according to CM theory, because mental activities are based on the functions of Qi and Blood (governed by the Heart). In addition, a disharmony of the Internal Organs may cause an emotional imbalance too.

Table 2.4 Relationships between the emotions and the Internal Organs

Emotions	Organs	Effects on Qi	Symptoms
Anger	Liver	Ascending Qi	Headache, dizziness, tinnitus, flushed face, haematemesis, even sudden fainting
Joy	Heart	Slowing down Qi	Palpitation, over-excitability, insomnia, even mental disturbance
Sorrow	Lung, Heart	Dissolving Qi	Shortness of breath, depression, fatigue, a discomfort feeling in the chest
Anxiety	Lung, Spleen	Stagnating Qi	Uncomfortable feeling in the chest, weak voice, poor appetite, abdominal distension, pale complexion
Thought	Spleen	Stagnating Qi	Poor appetite, abdominal distension, tiredness, pale complexion
Fear	Kidney	Sinking Qi	Incontinence of urine and stools, even syncope
Fright	Heart	Scattering Qi	Palpitations, breathlessness, insomnia, or mental confusion

2.3.1.3 Non-Internal/External causes of disease

Besides the previously mentioned pathogenic factors there are also some other factors which can cause disease. They include a weak constitution, excessive physical work, excessive sexual activities, irregular food intake, traumatic injuries, parasites and poisons, and pathological products such as phlegm and blood stasis. These may cause abnormal consumption or deficiency of the vital substances such as Qi, Essence and Blood, resulting in disharmony of Yin and Yang in the body.

2.3.2 Pathogenesis

Pathogenesis is the development or the mechanism of a disease, and refers to the origin of a disease and the chain of events leading to that disease due to a series of changes in the structure and/or function. Unlike western medicine, CM does not explain how a disease process arises at a microscopic level based on a series of changes in a cell/tissue/organ being caused by a microbial, chemical or physical agent. It holds that the occurrence of disease is due to the breakdown of the body's normal state of Yin and Yang balance (the disharmony between Yin and Yang) due to the influences of certain pathogenic factors, which can be external or internal or non-external/internal causes.

The pathogenesis of disease in CM is understood using a combination of the theories mentioned previously. The basic mechanism of disease is considered as the process of struggle between the ‘healthy Qi’ (a general term indicates the various types of Qi that protect the body) and pathogenic Qi. There are three kinds of conditions can be found during the conflict between healthy Qi and pathogenic Qi. One is the ‘Excess Syndrome’ referring to the presence of a pathogenic factor that is strong whilst the healthy Qi is still intact. The second is the ‘Deficient Syndrome’ which indicates the presence of a pathogenic factor with a deficiency of healthy Qi. The third is the mixed Excess/Deficient Syndrome.

However, all kinds of changes that occur in disease pathogenesis are usually linked to the mechanism of the Zang-Fu organs since these are responsible for the physiological functioning of the body. The pathogenesis is often analysed according to Qi movement in Organs (whether it is moving in the correct direction), Meridians and other parts of the body. For example, when Stomach Qi ascends instead of descending, it causes nausea, or vomiting. If the Qi fails to ascend in the Yang Meridians of the arm, the muscle below that area will feel numbness. If the Qi enters the nose excessively, there will be runny nose with profuse discharge.

Nevertheless, an imbalance between Yin and Yang is still the fundamental foundation of CM pathogenesis, and every mechanism of disease development can also be categorised into Excess/Deficiency of Yang, or Excess/Deficient of Yin.

2.4 Diagnosis

CM diagnosis is strong in its holistic view of the body and mind. The process of CM diagnosis is the collection of patient information through taking a case history and an overall observation of symptoms and signs, analysis of these according to several CM theories and drawing a conclusion about the disease and CM Syndrome.(Deng et al., 1984, Maciocia, 2004) There are four diagnostic methods used in CM diagnosis: Inquiry, Inspection, Auscultation/Olfaction, and Palpation. Based on the information obtained by the four diagnostic methods, by the process of Syndrome Differentation, CM practitioners describe the disharmonies in terms of the patterns of disharmony that manifest. There are several theories used in Syndrome Differentiation, like Zang-Fu Theory, Meridian Theory, Triple Jiao Theory, Theory of Qi, Blood and Body Fluids.(Deng et al., 1984)

2.4.1 The four diagnostic methods

2.4.1.1 Inspection

Inspection is a method to collect (visual) information about a patient by observation of the mental state, facial expressions, physical appearance, colour of the complexion, and any abnormal changes of secretion and excretion. Diagnosis by inspection in CM is based on the holistic view that the disharmonies of the Internal Zang-Fu Organs manifest themselves externally.(Maciocia, 2004) In general, inspection can be categorized into three components: inspection of the patient's vitality and complexion; inspection of body parts and inspection of the tongue.

Although the patient's physique can be classified using both Yin-Yang Theory and Five Element Theory, in clinical practice it is more important to observe the patient's mental and physical activities. In CM, the Mind and Spirit are formed from the Essence of the parents and nourished by the Essence of food and water taken in by the body. Therefore, the state of the 'Spirit' (or Shen) can indicate abundance or weakness of the vital substances, the constitution, and Yin/Yang in the body. Different sections of the face as well as different colours of the complexion correspond to different Zang-Fu organs. As for the inspection of the body parts, it is also based on the theory that each single part of the body can reflect the physiological and pathological change of the whole body.

Tongue diagnosis is a very important part of inspection, and it is regarded as a reasonably objective tool amongst the many diagnostic techniques in CM.(Maciocia, 2004) It includes inspection of the colour and shape of the tongue body, and the presence and colour of the tongue coating. The tongue has many relationships and connections to the Meridians and the Internal Organs. It can present a strong visual indicator of a person's overall state of harmony or disharmony. In CM, the tongue body shape reflects the state of Blood and Nutritive Qi, and indicates Excess or Deficient conditions. Constitution can also affect the shape of the tongue body. Tongue body moisture reveals the state of Yin and the Body Fluids in the body. The colour of the tongue body indicates the state of Blood and Yin organs, the presence of Heat or Cold in the body, and the conditions of Yin or Yang deficiency. The tongue coating indicates the state of the Yang organs, especially the Stomach, and also reflects conditions of Heat or Cold. Due to a special relationship with the Heart (that 'commands Blood'), the normal tongue has a light red or pinkish body with a thin white coating.

2.4.1.2 Inquiry

The consultation between the doctor and patient is the fundamental art in medicine. In CM, this is even more important since the CM diagnosis does not rely on medical diagnostic tests (as are used in orthodox medicine).(Lu et al., 2005) Inquiry is important not only to find out about the patient's life and symptoms, but also to find the causes of the disease and underlying disharmony or Syndrome. Although different CM practitioners may place emphasis on different questions, there are ten generally accepted questions that should be included in a case history, in addition to asking about the patient's lifestyle and family history.(Deng et al., 1984) These ten questions, called the 'Ten Rhythmic Questions' are about the presence of chills and fever; sweating; pain in the head or body; discomfort in the chest and abdomen; hearing and sight; appetite, presence or absence of thirst and any taste in the mouth; sleep; urination and defecation; and for women, questions about their gynaecological history and if relevant, children.(Deng et al., 1984)

2.4.1.3 Auscultation/Olfaction

In conventional medicine, tools like the stethoscope have been widely used in the physical examination. However in CM, traditional methods of auscultation and

olfaction are still used to make a judgement of the patient's condition. This kind of diagnosis, based on hearing and smelling, is based on the holistic view that the sound of the voice, breath sounds, coughing and body odors are related to the various Zang-Fu Organs, as explained in Five Element Theory. According to CM, all sounds are produced by Qi movement, so the strength and quality of the voice, pathological breathing sounds and coughing can indicate the state of the Qi and Body Fluids in the body, and can help differentiate between 'Exess' and 'Deficient' Syndromes.

2.4.1.4 Palpation

The diagnostic methods of palpation include palpation of the pulse, the head and neck, chest and abdomen, muscles, skin, extremities, and acupoints. Pulse diagnosis has been developed to a very sophisticated level in CM. It involves palpation of the pulse at the radial artery of both wrists, assessing the characteristics of the pulse and interpreting these in relation to the functional and physiological state of the internal organs.

In performing pulse palpation, the practitioner places the index, middle, and ring fingers on the radial artery, corresponding to distal (cun), middle (guan) and promixal (chi) part of the radial artery. The pulse positions are assigned to particular Zang-Fu Organs. The correspondences are listed in Table 2.5.

Table 2.5 Correspondence of pulse positions to Zang-Fu Organs

	Cun	Guan	Chi
Left	Heart and Pericardium	Liver and Gall Bladder	Kidney and Bladder
Right	Lung	Spleen and Stomach	Kidney

The pulses are palpated at three levels, superficial (located with light touch), middle (located using medium pressure) and deep (pressing almost to the bone with a heavy pressure) in order to detect three different levels of Qi (energy) flowing the body. In general, the superficial level indicates the state of the Qi and Yang (Fu) Organs, the middle level indicates the state of Blood, and the deep level indicates the state of Yin in general and Yin (Zang) Organs. The strength of the pulse can reflect the imbalance

of Yin-Yang and indicate if a condition is one of Excess or Deficiency. The clinical significance of the pulse strength is set out in the Table 2.6.

Table 2.6 Clinical significance of the pulse strength at the three levels

	Superficial	Middle	Deep
Weak	Yang or Qi deficiency	Blood deficiency	Yin deficiency
Strong	Invasion of external pathogenic factors; or Excess of Yang	Blood Heat; or Blood stasis	Cold or Heat or stasis in the Internal Organs

In traditional terms, there are 28 pulse classifications of pulse, which describe the way the pulse feels underneath the fingertip. Each pulse quality has a particular clinical significance, and there are pulse combinations too. Therefore, the pulse gives CM practitioners a general picture of disharmonies within the body and the state of Qi and Blood as a whole. Pulse and tongue diagnosis are considered to be the 'two pillars' of the four examination methods in traditional practice. It is understood that the accuracy of pulse diagnosis is associated with the skill level and experience of the CM practitioner.

2.4.2 Syndrome differentiation

Syndrome Differentiation refers to the diagnosis process of Syndrome diagnosis through comprehensive analysis of symptoms and signs to determine the cause, nature and location of the disease. Syndrome diagnosis then guides treatment.(WHO, 2007)

The concept of 'disease' in CM is broad and can include symptoms or signs. For example, in CM 'abdominal pain' has several CM Syndromes, yet abdominal pain is a symptom associated with several biomedical diseases such as ulcerative colitis or irritable bowel syndrome. The one disease may manifest with different Syndromes and the same Syndrome may be seen in many different diseases.

Although disease diagnosis is also important in CM, Syndrome Differentiation is emphasised and widely applied in CM. There are several methods and theories used to

identify the CM Syndrome. Amongst these, the Eight Guiding Principles and Zang-Fu Theory are the most important methods to differentiate CM Syndromes.

2.4.2.1 The Eight Guiding Principles

Syndrome Differentiation according to the Eight Guiding Principles is the foundation for all the other methods of the identification of Syndromes. It refers to categorisation of a patient's condition according to four opposing pairs of principles: Interior/Exterior, Heat/Cold, Excess/Deficiency and the overall summary principles of Yin/Yang.

The patterns of Exterior and Interior refer to the location of the disease. Hot and Cold describe the nature of a Syndrome in terms of temperature. Excess and Deficiency indicate the presence or absence of a pathogenic factor and the strength of the body's energy (as described previously). Yin and Yang summarise and categorise the other six principles: Interior, Cold and Deficiency are Yin in nature, whilst Exterior, Hot and Excess are Yang in nature. However, it is important to bear in mind that the Eight Guiding Principles are not mutually exclusive, and they could be inter-related, or combined or may convert into each other. For example, a Syndrome of Wind-Heat invasion (Exterior-Heat) could cause Deficiency of Lung Yin (Deficient-Heat) if the heat consumes the Yin body fluids.

2.4.2.2 Syndrome differentiation according to Zang-Fu Theory

The Eight Guiding Principles form the preliminary analysis. If a more detailed analysis and identification the involved Organs of a disease is required (and in order to better guide treatment), the method of Syndrome Differentiation according to Zang-Fu Theory is more useful, particularly for interior and chronic diseases.

The first stage of Syndrome identification according to Zang-Fu Theory is to identify which organ(s) have been affected. This is done so by understanding the Organ functions and Organ-to-Organ relationships and knowing the typical clinical manifestations of disharmony in the particular Organs, in addition to the correspondences between human body, Organs and the Five Elements (see Table 2.2 and Table 2.4). Once the affected Organ(s) are identified, the relative states of Yin, Yang, Qi, and Blood can be determined via the application of the Eight Guiding Principles and the pattern identification of Qi, Blood and Body Fluids. Once a picture

has been made of the presenting disease through those methods, a conclusion can be made as to the underlying CM Syndrome. An example of a CM Syndrome is 'Syndrome of Liver Blood deficiency'.

2.5 Treatment

Consideration is given to both the underlying or root cause of an illness ('ben') and the clinical manifestations or 'branch' ('biao') in deciding the treatment principle. The concepts of 'ben' and 'biao' are not quite straightforward however. In terms of aetiology and symptoms, the cause of disease is 'ben' and the symptoms are the 'biao'. In terms of the sequence of diseases, the older disease or primary disease is considered the 'ben' whilst a new or secondary disease is 'biao'. In the expression 'concentrating treatment on the root cause', the emphasis is on the 'ben' since there may be many clinical manifestations but only one root cause and it is believed that if you find the root cause, you can successfully treat any disease no matter how complicated.

There are two main therapeutic modalities in CM, acupuncture and Chinese herbal medicine (CHM). Since this thesis is mainly concerned with CHM, this section will focus only on CHM. Acupuncture has been discussed in the section on the Meridian Theory.

2.5.1 Chinese herbal medicine

Chinese herbal medicine (CHM) is one of the important modalities utilised in CM clinical practice. In particular, it is guided by Five Element Theory and Meridian theory.

There are several different methods used to classify traditional Chinese herbs. The 'Four Natures' and the 'Five Tastes' are the most common methods. The Four Natures refer to the temperature characteristics of herbs which are hot, cold, warm, and cool. However there are actually more than four descriptions of the temperature characteristic including neutral, slightly cold, and slightly warm. These descriptions could be considered subjective because they are based on people's reaction to the herb.(Bensky et al., 2004) Subsequently, there may be different descriptions of the same herb in different texts.

The Five Tastes is another method of categorising Chinese herbs. The Five Tastes are pungent, sweet, bitter, sour and salty. However, there are also some medicines (or food) which do not have those tastes and they are said to be bland. Furthermore, the term ‘astringent’ is included as a ‘taste’. Therefore, this ancient concept of taste pertains more to a category rather than an objective property.

In CM, the taste and temperature characteristics of an herb have specific effects and partly determine its therapeutic function. The pungent taste has the effect of dispersing and moving. The sweet taste has the property of tonifying and harmonising or moistening. Bitter implies draining and drying. Sourness is astringing and can counter the abnormal leakage of fluids and energy. The salty taste has an action of purging and softening (hardness). The bland taste can promote urination and eliminate dampness. The theory of taste and temperature has a close relationship to the concept of correspondence between nature and human, the pivotal theory of CM. The temperature characteristic of herbs is related to ‘Heaven’ (this actually refers to climate), and the tastes are related to ‘Earth’. Therefore, different seasons, climate or quality of the earth are understood to influence the chemical ingredients of herbs causing different therapeutic functions. (Tang et al., 2010) This theory also represents the philosophical thinking in CM, ‘harmony among Heaven, Earth and Man’, in other words, the relationship between human beings and natural environment. The herbs are part of nature, so herbs should be matched to the pattern of disharmony when they are prescribed to remedy the imbalance in the human body.

Another way of categorising herbs in CM is to identify which Meridian it enters. It is an attempt to describe the main therapeutic actions of an herb in relation to the pathological changes in particular Meridians and Organs. In other words, the herb could focus the effect of a formula onto a specific Meridian and its corresponding Organ where the disease occurs. Typically one herb may enter several (1-3) meridians.

In the standard Materia Medica, herbs are usually categorised by their main therapeutic functions which can correct a certain disharmony. Each herb has a primary function for which it is categorised, plus typically two-three other actions for which it may be chosen. For example, there are herbs that ‘regulate the Qi’, ‘tonifying’ herbs, herbs that ‘drain Dampness’ to name a few. In addition, the function of herbs in certain categories can be understood from a biomedical perspective. For example,

‘herbs that drain Dampness’ are usually herbs with a diuretic function whilst herbs in the category of ‘Clear Heat & Relieve Toxicity’ have antipyretic and anti-inflammatory functions.(Bensky et al., 2004)

In CM, herbs are seldom used alone, and usually combined into a formula. Formulae are carefully and logically constructed according to a fixed structure. However, the art of combination is the selection of the herbs. One or two herbs will play the major role in the prescription, and they may make up the largest proportion in the formula. Several other herbs assist the main herbs to treat the secondary disharmony. According to tradition, those different roles are named Chief, Minister, Assistant and Guide. The Chief herb has the major therapeutic effect and is indispensable to the formula as it contributes the most critical effect on the primary CM Syndrome. The Minister herb aids the Chief herb in addressing the primary Syndrome and may also have an effect on the secondary Syndrome. The Assistant herbs moderate the strength of the main herbs, and may be used to address secondary symptoms and signs. The Guide herbs usually harmonise the actions of other herbs in the formula, and/or direct the formula to particular Organs and/or Meridians.

The selection and combinations of herbs are all based on CM theory and the individual herbal properties. In addition, there are seven types of herbal combinations that are distinguished by their effects. These are mutual accentuation (the combination of the two herbs accentuates their therapeutic actions), mutual enhancement (the combination of two herbs which have different actions enhances the effect of one of them), mutual counteraction (the combination of two herbs reduces the side effects of one herb by another herb), mutual suppression (similar to mutual counteraction but emphasises on the action of the herb which can reduce the side effects), mutual aversion (the combination of two herbs minimises the positive effects of one herb due to the other), and mutual incompatibility (the combination of two herbs leads to toxicity).(Bensky et al., 2004)

Much research has been completed on the functions of active constituents of Chinese herbs and on individual medicinal formulae from the biochemical, pharmacological and biomedical perspectives. In modern CM, some practitioners also take into account the function from these perspectives in selecting herbs for combination in a formula. However, the formulation of the CHM formula is mainly guided by traditional theory.

As for the forms of herbal medicines, decoction of raw herbs is the most common form, which extracts and concentrates ingredients by boiling the herbs in water. There are also other forms like granules, liquid extracts, pills, powders, ointments, and medicinal wine.

2.6 Conclusion

The modalities of CM include acupuncture, herbal medicine, massage, dietary advice and exercise. The underlying principles of CM are very different from western notions about health, illness and the workings of the body. The ancient Chinese proposed that every living thing is sustained by a balance of two opposing but complementary forces of energy, called Yin and Yang, and composed of five elements found in nature: Fire, Earth, Metal, Water and Wood. The vital substances like Qi, Blood and Body Fluids flow through the body via invisible Meridians to connect with the Internal Organs. Any disease is diagnosed and treated according to the differentiation of the pattern of disharmony in the Internal Organs and Meridians. The treatment is of both the disease and CM Syndrome or pattern of disharmony. The process of Syndrome Differentiation is the process of analysis of signs and symptoms according to the several theories, the major ones being the Eight Guiding Principles and Zang-Fu Theory. As a result CM treats the entire mind and body rather than one or the other and also recognises the link between the human body and the external environment. Treatment is aimed at both the disease and, in particular, the CM Syndrome.

Chapter 3 Pharmacologic and Non-Pharmacologic Treatment of Osteoarthritis

3.1 Introduction

The management goals of patients with osteoarthritis (OA) are to control pain and other symptoms, minimize disability, and educate the patient and his or her family about the disease and its therapy.(Hochberg et al., 1995) Although there is no known cure for OA, treatments designed for the individual patient include the use of non-pharmacologic modalities and the use of pharmacologic agents. Non-pharmacologic therapy retains its primacy and position as the base upon which other modalities may be added.(American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000) However, many patients with OA find that non-pharmacologic intervention alone does not allow them to improve joint function and health-related quality of life adequately, while pain restricts mobility and willingness and ability to undertake any form of physical activity. Hence, pharmacologic treatment is usually an important and essential next step. Because of the chronic nature of OA, safety is a critical factor in distinguishing among various effective pharmacologic therapies.

There are various approaches to non-pharmacologic and pharmacologic therapies. Pharmacologic therapies refer to currently available therapeutic agents including intra-articular injections (e.g., hyaluronic acid, corticosteroid), non-opioid analgesics (e.g., acetaminophen), topical analgesics (e.g., capsaicin and methylsalicylate creams), non-steroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics (e.g., propoxyphene, codeine, oxycodone). Non-pharmacologic therapies usually include physiotherapy, physical exercise, weight loss, education intervention, joint protection devices, thermal modalities, self-management and social support. The American College of Rheumatology (ACR) publish guidelines for the treatment of OA of the knee. They recommend that for mild symptomatic OA treatment could include non-pharmacologic methods and pharmacologic therapies (including oral or topical application). For moderate OA they recommend that the use of NSAIDs is appropriate and for those with joint swelling, intra-articular injection may also be used. In the case of severe OA, the guidelines suggest that surgery may be required.(American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000, Hochberg et al., 1995)

In this chapter, the clinical efficacy and safety of the most commonly used pharmacologic agents and non-pharmacologic therapies will be discussed.

3.2 Pharmacologic agents

3.2.1 Acetaminophen

ACR Guidelines (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000) for the medical management of OA emphasise the initial use of the pure analgesic, acetaminophen, as the first choice in patients with OA who require pharmacologic intervention. This is based on the fact that acetaminophen provides effective relief of pain and has been demonstrated to be safe in a wide range of populations.(American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000, Hochberg et al., 1995, Temple et al., 2006) The study of Temple and colleagues (Temple et al., 2006) indicated acetaminophen was generally well tolerated in patients for the treatment of OA pain for periods of up to 12 months; even despite receiving at, or near, the maximum recommended daily dose for $\geq$ 180 days. No clinical abnormalities in liver or renal functions were observed. The pervasive belief contends that acetaminophen is not only effective in treating OA pain but is of equal analgesic efficacy as NSAID drugs.

However, some available data suggest that acetaminophen has better clinical efficacy than placebo but is statistically inferior to traditional NSAIDs and cyclooxygenase (COX) -2 specific inhibitors. (Battisti et al., 2004, Geba et al., 2002) In addition, results of a survey indicated there was a considerable and statistically significant preference for NSAIDs compared with acetaminophen among three groups of rheumatic diseases patients, with 21% of 479 patients with OA treated with acetaminophen reporting that the agent was not effective in relieving their OA pain and 38% reporting that it was only slightly effective.(Wolfe et al., 2000). Furthermore, there is a commonly held belief that patients with inflammatory OA (clinically defined by the presence of detectable effusion) may respond better to NSAIDs.(Pelletier et al., 2001) Therefore, there is an argument that NSAIDs may be warranted as initial pharmacologic therapy rather than Acetaminophen. A randomised, double-blind, placebo-controlled trial that compared Acetaminophen, the NSAID Diclofenac and placebo demonstrated superior efficacy of Diclofenac over acetominophen.(Case et al., 2003)

3.2.2 Non-steroidal anti-inflammatory drug

The NSAIDs represent the largest range of drugs, and include salicylates, propionic acid substitutes such as Ibuprofen and Naproxen, and acetic acid derivates such as Diclofenac and Indomethacin. Standard therapy for patients presenting with painful symptoms or musculoskeletal disorders are NSAIDs which belong to the group of rapid-onset symptom-modifying drugs. They are widely prescribed as a basic medication throughout the world for OA as the efficacy is well-established.(Hedner and Everts, 1998)

NSAIDs have been developed during the past two centuries since salicylate was discovered in the mid 19th century. Most NSAIDS were initially organic acids, but later non-acidic compounds were discovered. The first stage of NSAIDs discovery was the pre-prostaglandin period in the 1970s, but drugs such as Aspirin, Indomethacin and Phenylbutazone have been shown to cause gastrointestinal (GI) side effects.Since the late 1980s, an important discovery was made from molecular and cellular biological studies that there are two cyclooxygenase (COX) systems controlling the production of prostanoids [prostaglandin (PG) and thromboxane (TX)]. This discovery was made following screening for anti-inflammatory, analgesic and antipyretic activities in laboratory animal models. Each prostanoid is encoded by a separate gene and exhibits a discrete pattern of tissue-specific expression.(Rainsford, 2007) Most of the therapeutic effects of NSAIDs, as well as their side effects, are due to their ability to inhibit COX, a key enzyme in prostaglandin synthesis.(Everts et al., 2000) COX-1 is predominantly expressed continually and functions as a physiologic 'housekeeping' enzyme in most tissues. It is involved in protection of the gastric mucosal integrity, platelet aggregation, vascular homeostasis, and maintenance of renal sodium-water balance.(Fendrick and Greenberg, 2009) COX-2 expression, especially in macrophages and synovial cells, is induced by inflammation and mitogen stimulation. It has been proposed that the anti-inflammatory properties of NSAIDs are mediated through COX-2 inhibition, whereas adverse effects of NSAIDs occur as a result of their influence on COX-1.(Lichtenstein and Wolfe, 2000)

The hypothesis of COX isozyme selectivity has led to a proposed classification for COX inhibitors: COX-1 selective inhibitors (low-dosage Aspirin), COX non-selective inhibitors (the majority of classified NSAIDs), and COX-2 preferential inhibitors (e.g.

Meloxicam and Nimesulide), which have fewer gastric side effects than standard NSAIDs, but are not risk-free at high doses, as well as COX-2 selective inhibitors (e.g. Celecoxib and Rofecoxib). The World Health Organisation (WHO) has categorised COX-2 selective drugs as coxibs, a new subclass of NSAIDs.(Vane and Warner, 2000)

In contrast to the previous recommendation that Acetaminophen was the drug of choice for the initial treatment of all patients with OA, new opinions support consideration of the use of NSAIDs as initial treatment, either COX-2 selective inhibitors or classical NSAIDs with gastroprotective agents, particularly in patients with moderate to severe pain and inflammation.(Moskowitz, 2001) NSAIDs were not recommended as first-line therapy in a guideline published by the American College of Rheumatology (ACR) in 1995 due to toxicity concerns, primarily involving the gastrointestinal (GI) tract as well the kidneys and other organs. NSAID-related ulcer complications termed POBs (perforation, gastric outlet obstruction and bleeding) were estimated to lead to at least 103,000 hospitalisations and 16,500 NSAID-related deaths among patients with rheumatoid arthritis (RA) or OA every year in the United States, and constitute the 15th most common cause of death in the United States.(Wolfe et al., 1999) GI side effects are also the primary reason individuals discontinue NSAID medications. For those reasons, coxibs are the drugs of choice in patients at high risk for developing GI toxicity or bleeding.(Laine et al., 2007, Sheldon et al., 2005, Silverstein et al., 2000)

Coxibs may be utilised in at least three clinical circumstances for pain relief in patients with OA. First, these agents can be used in patients who have had an inadequate response to non-pharmacologic modalities and to maximum doses of Acetaminophen. Second, they can be used as initial therapy in patients with more severe pain who require a greater magnitude of pain relief than commonly obtained with Acetaminophen, or in individuals with pain and signs of effusion of joints. Finally, coxibs can represent a potential medication in patients on anti-coagulative therapy or preoperative period.(Schnitzer, 2002)

Although COX-2 selective NSAIDs appear to be new and improved, they are less than perfect. Some clinical studies and surveys showed rates of thrombotic cardiovascular events in patients with arthritis on Etoricoxib were similar to those in patients on the traditional NSAID Diclofenac. COX-2 inhibitors also carried a risk of

cardiovascular side effects among elderly patients, and there was a lack of proof of a lower long-term risk of GI toxicity with COX-2 inhibitors.(Bouee et al., 2004, Cannon et al., 2006, Modica et al., 2005) On the other hand, alternatives to coxibs for minimising GI side effects in OA patients do exist. For example, the use of a gastroprotective agent (e.g. Misoprostol twice or three times daily or enteric-coated enzyme tablet) in combination with an NSAID offered substantial protection against gastric and duodenal ulcers in patients receiving NSAID therapy.(Akhtar et al., 2004, Raskin and White, 1995) However, the addition of a gastroprotective agent means additional pills, additional costs, and the potential for additional side effects.

Although COX-2 selective inhibitors, such as Celecoxib, Rofecoxib, Meloxicam and Valdecoxib, demonstrate fewer GI side-effects than non-selective NSAIDs, these COX-2 selective drugs act in a similar problem with non-selective NSAIDs at the level of the kidney, with reduced excretion of electrolytes secondary to adverse renal effects, as well as progression to hypertension.(Harirforoosh et al., 2006, Schnitzer, 2002) Use of NSAIDs or coxibs in patients at high risk for developing congestive heart failure (CHF) should also be undertaken with caution. In May 1999, a trial reported a five-fold increase in thrombotic cardiovascular events among patients treated with 50 mg/d of Rofecoxib, compared with 1g/d of Naproxen, after its approval by the US Food and Drug Administration (FDA). Subsequently, in 2004, Merck withdrew Rofecoxib from the market after its trial showed a two-fold increase in CV risk with 25mg/d of Rofecoxib compared with placebo.(Bombardier et al., 2000, Merck, 2004) Similarly, a Pfizer study showed an increase in cardiovascular risk with Celecoxib.(Prizer, 2006) Furthermore, the Australian Therapeutic Goods Administration (TGA) cancelled the registration of Lumiracoxib in August 2007 because of serious liver side effects associated with the use of the drugs which had resulted in eight cases of serious liver adverse reactions, including two deaths and two liver transplants since it was approved in Australia in July 2004.(Australia Therapeutic Goods Administration, 2007)

It may be difficult to ascertain the clinical safety of the COX-2 inhibitors, for example, rates of cardiovascular adverse events, in the absence of long term studies. Such studies are important because COX-2 inhibitors are usually prescribed for long-term use. The longer a drug is to be used by a patient, the more seriously the question of potential effects on the cardiovascular or other systems must be taken. One clinical

trial and a systematic review demonstrated that there was no difference between Rofecoxib, compared to non-selective NSAIDs (Ibuprofen, Diclofenac, or Nabumetone) and placebo in the risk of cardiovascular thrombotic events,(Reicin et al., 2002, Weir et al., 2003), however caution should be taken because the trial and the review were funded by Merck Research Laboratories.

In summary, coxibs offer an important new alternative to NSAIDs for the treatment of OA. In patients in whom Acetaminophen and non-pharmacologic therapies do not adequately control pain, coxibs provide a safe and effective intervention, but it should be considered based on the patient's medical background, tolerance of serious side effects, and cost of this form of therapy. The safety and drug-interaction profiles of the current available COX-2 agents should be considered during clinical selection, as well as the likelihood of sustained long-term use.

3.2.3 Opioid analgesics

Pain is a major cause of disability in patients with OA, and opioid treatment has been extended to patients with this kind of chronic pain after it proved indispensable for management of acute and terminal cancer pain. Opioid analgesics, which include opioids and Tramadol (an opioid agonist and centrally acting analgesic not chemically related to opioids), have been recommended by the American Pain Society as a safe and effective therapeutic option for the treatment of moderate to severe chronic OA pain that does not respond to first-line agents.(Kivitz et al., 2006)

Formulations of those opioids which release the drug and maintain analgesia over an extended period rather than immediate-release formulations are preferred because they are able to provide consistent stable analgesia and convenient dosing. This is associated with decreased frequency of sleep interruptions, reduction in dependence on caregivers, and improved compliance. A randomised, placebo-controlled, dose-ranging, Phase III study in patients with OA-related pain of the hip and knee who had a suboptimal response to such first-line analgesic agents, suggested that Oxymorphone extended release (ER) was an effective treatment for improving measures of pain, function and quality of life, and the analgesia was dose dependent.(Kivitz et al., 2006) In that trial, the improvements in pain observed with each dose of Oxymorphone ER exceeded the conventional criterion for clinically meaningful pain relief, a change of ≥ 15 mm on a 100 mm visual analog scale (VAS).

This supported the findings of a previous short-term (4 weeks) trial of Oxymorphone ER tablets which demonstrated taht doses of 20mg and 40mg twice daily provided superior pain relief and functional improvement relative to placebo.(Matsumoto et al., 2005)

Other research on Hydromorphone (a hydrogenated semisynthetic ketone of morphine) and Oxycodone indicated approximately two thirds of patients in Hydromorphone group and Oxycodone group (67.2% and 66.7%, respectively) rated the overall effectiveness of treatments as 'good' to 'excellent' at end point, with no statistically significant differences between groups in total scores of Western Ontario and McMaster University osteoarthritis index (WOMAC).(Hale et al., 2007) Tramadol is a drug combining noradrenergic, serotonergic and mild opioid action. A 12-week double-blind, placebo-controlled study demonstrated Tramadol ER, when given as a dose of 200 to 400 mg once a day, resulted in significant improvements in the symptoms of OA by outcome measurements including a pain intensity visual analogue scale (VAS), WOMAC scales and patient global assessment.(Babul et al., 2004)

However, opioid treatment of pain has been hampered because of actual and legal constraints related to additional risk. There is a lack of efficacy and demonstration of the safety profile of opioids in the long-term treatment of OA, even though GI and central nervous system adverse events like nausea, constipation, somnolence and dizziness have been observed (Babul et al., 2004, Hale et al., 2007, Kivitz et al., 2006, Matsumoto et al., 2005) The complications of long-term opioid use are more insidious, complex and poorly understood, and include hormonal and immune effects and addiction. Opioid drugs may affect immunity through their neuroendocrine effects, or through direct effects on the immune system.(Ballantyne, 2006) Addiction in particular is an important problem, with related legal considerations and moral and ethical dilemmas. The best way to help patients needing opioid treatment for OA is to provide the treatment in a cautious, selective and supportive manner.

3.2.4 Topical treatment

Topical treatment is an additional option for patients with OA who have inadequate pain relief or who cannot tolerate systemic therapy. Formulations for topical application can be creams, lotions, gels, aerosols or patches. These therapies may

allow for a higher local concentration of drug at the site of the pain with minimal systemic absorption by targeting a site immediately adjacent to or in close proximity of the site of application. Studies on peripheral pain signaling in animal models of OA (Laird et al., 2001, Veneroni et al., 2003) have suggested that the up-regulation of sodium channel expression in primary afferent neurons induced by joint inflammation may be an important mechanism involved in chronic OA pain. Medications applied topically to control pathophysiologic peripheral pain responses will act locally on peripheral nerves or on damaged or dysfunctional soft tissues to elicit an analgesic response.(McCarberg and D'Arcy, 2007)

The best evaluated topical agents in the medical management of OA are NSAIDs and capsaicin. NSAIDs have been applied topically for decades, and some of them are available without prescription. They are widely advertised for acute and chronic painful conditions as over the counter (OTC) medicines. A systematic review and meta-analysis of topical NSAID trials concluded that those drugs were effective in treatment of acute soft tissue injuries (like strains, sprains or sports injuries) and chronic musculoskeletal conditions (like OA and tendonitis).(Mason et al., 2004b, c) Although the sample sizes were small and the studies of variable quality, some randomised controlled trials of topical NSAIDs indicated that they were significantly more effective than placebo for pain relief, and that the efficacy was not just due to rubbing.(Baer et al., 2005, Bookman et al., 2004, Roth and Shainhouse, 2004)

The most published papers relating to topical NSAIDs are on the Diclofenac solution, which consists of 1.5% (wt/wt) Diclofenac sodium, 45.5% (wt/wt) dimethyl sulphoxide (DMSO), which enhances the in vitro percutaneous absorption of Diclofenac, propylene glycol, glycerine, ethanol and water. The results of these trials indicated superior therapeutic benefits of topical Diclofenac solution compared with the vehicle-controlled solution (containing 45.5% DMSO, no Diclofenac) and the placebo solution (containing 4.55% DMSO, no Diclofenac). The improvement of WOMAC scores in the treatment group ranged from 35% to 46% over baseline values.(Roth and Shainhouse, 2004) Safety analyses revealed no apparent, serious adverse effects after treatment with the topical Diclofenac solution, with reversible dryness on the application-site skin the main complaint.(Bookman et al., 2004, Roth and Shainhouse, 2004) The low incidence of systemic adverse effects for topical NSAIDs probably results from the much lower plasma concentrations from similar

doses applied topically compared to those administered orally.(Moore et al., 1998, Rolf et al., 1999)

One implication of short duration studies, however, is that they will not capture important long-term safety information. This may be important for ongoing application of gels, creams or sprays. The risks of topical NSAIDs may not be negligible. A record linkage case-control study showed there have been seven reports of adverse events in the GI tract after topical application of Diclofenac since 1963, four with Ibuprofen, one with Ketoprofen, 25 with Piroxicam and 47 with Felbinac.(Evans et al., 1995) In addition, a meta-analysis of 13 trials showed that research evidence to support the long term use (more than one month) of topical NSAIDs in OA is absent,(Lin et al., 2004b) though an equivalence trial demonstrated application of this topical Diclofenac solution to the knee of patients with OA produced relief of symptoms equivalent to oral Diclofenac.(Tugwell et al., 2004) Therefore, larger and longer trials are necessary to fully clarify the place of topical NSAIDs in clinical practice.

The use of capsaicin from chilli peppers as an analgesic is not new. Randomised controlled trials comparing topical capsaicin with placebo or other active treatments for neuropathic pain started in the late of 1980s.(Derry et al., 2009) Capsaicin binds to nociceptors in the skin, causing excitation of neurons and a period of enhanced sensitivity, followed by a refractory period with reduced sensitivity. As such, it can be used to treat pain from neuropathic and musculoskeletal disorders. A systematic review (Mason et al., 2004a) of topical capsaicin for the treatment of chronic pain demonstrated topical capsaicin is better than placebo, but the efficacy estimates are low due to the difficulty in creating double blind conditions in those trials; many patients can recognise a stinging or burning sensation with treatment. Another study also indicated the pain of OA was decreased more effectively and was more tolerable with application of the combination of capsaicin and glyceryl trinitrate than either alone.(McCleane, 2000)

However, although the drug is applied to the skin, it does not necessarily have fewer adverse effects. With topical capsaicin, one third of the patients experienced local adverse events and one in ten withdrew from treatment.(Mason et al., 2004a). Despite this, it may be regarded as an adjuvant to standard treatment for neuropathic pain with

conventional or non-conventional analgesics, or it may serve as a last resource when everything else has failed.(Tramer, 2004)

3.2.5 Intra-articular injection

Intra-articular injection is considered a local therapeutic modality for patients with knee OA with significant disability and advanced radiographic disease who have not responded to more conventional treatments.(Gaffney et al., 1995) Corticosteroid and hyaluronic acid are the most frequently used intra-articular therapies in OA, though the management of them is controversial.

Corticosteroids are potent anti-inflammatory agents that act by several mechanisms: by impairing antigen opsonisation, interfering with adhesion of inflammatory cells and migration through the vascular endothelium, interrupting cell-cell communication by alteration of release, or antagonism, of cytokines (interleukin-1), impairing the synthesis of leukotrienes and prostaglandins, inhibiting the production of neutrophil superoxide, metalloproteinase and metalloproteinase activator (plasminogen activator), and decreasing immunoglobulin synthesis.(Uthman et al., 2003) Different corticosteroid formulations have been used over the years like Triamcinolone Acetonide, Methylprednisolone Acetate (MPA), Prednisolone Acetate and Phosphate-Betamethasone Acetate, in single or multiple repetitive injection regimes. Several studies support that contention that corticosteroids provide short term pain relief in knee OA, but there are still arguments as to whether local corticosteroids acting to relieve pain were also associated with reducing joint effusion (synovitis), which usually contributes clinical benefits.(Gaffney et al., 1995, Jones and Doherty, 1996, Leopold et al., 2003)

As for the safety and efficacy of long-term intra-articular steroid injections, a two-year follow-up trial indicated OA patients who received Triamcinolone Acetonide had a significantly greater change in the range of motion of the affected knee, and a slightly greater improvement in pain, compared with baseline than did the saline control patients, especially at the first year of follow-up.(Raynauld et al., 2003) The anti-inflammatory effect of synthetic glucocorticoid was considered as a basis for those effects. However, intra-articular injection is still controversial for fear that these injections, especially when used repeatedly as long-term treatment, could promote

joint destruction and tissue atrophy, and because the long term benefits have not been confirmed.(Bellamy et al., 2006)

Although hyaluronic acid is thought to last longer than corticosteroid treatment,(Brys, 2004) a comparison trial of intra-articular injection of corticosteroid and hyaluronic acid indicated that no difference was detected between the two modalities with respect to pain relief or function at six months follow-up.(Leopold et al., 2003) Further, Leopold and colleagues did not recommend hyaluronic acid as a first-line treatment for intra-articular injection owing to the need for more frequent injections and the associated higher risk, as well the greater expense compared with corticosteroids, although their conclusion has not gained universal support.(Brys, 2004, Leopold et al., 2003)

3.3 Non-pharmacologic therapies

Like pharmacologic therapies, current non-pharmacologic treatment strategies aim to reduce pain, physical disability and handicap, and some of them also attempt to limit structural deterioration in affected joints. Both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have developed recommendations for non-pharmacologic modalities for the management of mild systematic OA, which were based on a combination of expert consensus and systematic review of research evidence.(American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000, Pendleton et al., 2000) The updated appraisals of existing guidelines provided by the Osteoarthritis Research Society International (OARSI) (Zhang et al., 2008b, Zhang et al., 2010) also encourages patient-driven regimes of non-pharmacologic therapies for all patients with hip and knee OA. The recommendations from these three groups suggest the use of NSAIDs should be additional to non-pharmacologic therapy for patients who were unresponsive to those self-help modalities and organised exercise programmes.(Hochberg et al., 1995, Pendleton et al., 2000, Zhang et al., 2008b)

Regular physical activity and exercise are key components of OA management. Exercise therapy is a general concept which can be defined as muscular contraction and bodily movement. In addition, therapeutic exercise can also be distinguished by its content (e.g. muscle strengthening or functional activities), delivery mode (e.g. individualised or group based) and dosage (e.g. frequency, intensity and

duration).(Pisters et al., 2007) The most common exercise modalities include aerobic exercise, muscle strengthening exercise (resistance exercise), aquatic exercise, and Taichi (a form of Chinese exercise therapy). The choice of exercise modality should be individualised.(Lee and Shmerling, 2008, Brandt, 1998) For example, water-based exercise is especially favourable in over-weight patients with muscle weakness, minimising weight-bearing impact. However, there is less information about the long-term effects of exercise. A systematic review of long-term ($\geq$ 6 months after treatment) effectiveness of exercise therapy (Pisters et al., 2007) suggested that evidence of long-term effectiveness could be only found in the outcome of patient global assessment, but not in other outcomes like pain, self-reported physical function and observed physical function.

Overweight patients with knee OA are strongly recommended to lose weight or maintain weight at a lower level by all the guidelines.(American College of Rheumatology Subcommittee on Osteoarthritis Guidelines, 2000, Pendleton et al., 2000, Zhang et al., 2008b) A meta-analysis indicated physical disability could be significantly improved if patients could lose weight at the rate of > 0.24% reduction per week.(Christensen et al., 2007) The study also suggested the patient should reduce their body weight at least by 5% within 20 weeks in order to be able to experience clinically significant improvements in function.

Joint protection devices have been often used as non-pharmacologic therapies for OA patients as well, like knee braces, appropriate footwear and lateral wedged insoles for shoes. For patients of knee OA accompanied by varus or valgus instability, a knee brace can shift the joint contact force away and reduce pain.(Zhang et al., 2008b) Simliarly, the use of lateral wedged insoles for patients with medial tibio-femoral OA is believed to lower medial compartment load.(Sharma, 2002) However, a Cochrane review (Brouwer et al., 2005) showed there was limited evidence with respect to effectiveness of such devices- it found that a brace and a lateral wedged insole have a small beneficial effect as measured by the WOMAC, and there was no evidence that a brace is more effective than an insole. The long-term effects of those devices have not been verified yet.

Applications of superficial heat or cold have been widely used for pain relief in many OA patients. There were only three RCT studies related to thermotherapy that

satisfied the inclusion criteria of a Cochrane review.(Brosseau et al., 2003) The review found limited evidence of the effectiveness of thermotherapy. The included trials varied in terms of design, outcomes measured, therapeutic modalities and overall methodological quality, making it difficult to reach a conclusion.

There are very few good quality studies of non-pharmacologic therapies for OA compared with pharmacologic research. Non-pharmacologic therapies usually get less financial support to conduct large, well-designed trials, unlike pharmacologic therapies which are often funded by the pharmaceutical industry.(Perkins and Doherty, 1999) In addition, blinding is an important component to evaluate the study quality, but it is more difficult to blind patients, doctors and assessors in trials of physical therapies. Inadequate concealment of treatment or sham treatment could contribute to higher odds ratios, which has been identified as a concern in physical therapy studies.(Schulz et al., 1995)

3.4 Conclusion

The pathogenesis of OA is complex and not well understood. There are no curative therapies currently available for OA. Non-pharmacologic therapies and pharmacologic agents are still mainstream choices in western medicine. Most of the western drugs for OA target pain relief. In general, there are two main types of pharmacologic treatments for OA: acetaminophen which is used to relieve pain but does not affect joint effusion, and NSAIDs which can reduce pain and swelling. However, both are associated with side effects though it is not clear which of the two types of drugs cause more problems.

There are patients who are unresponsive to western pharmacologic treatment for OA, and unable to tolerate side effects of such medications. The use of complementary and alternative medicine (CAM) for treatment of OA and other rheumatological disorders has become popular in recent years. In the next chapter, the main forms of complementary medicines used in OA treatment, their mechanisms of action and the scientific evidence of efficacy is explored.

Chapter 4 Complementary and Alternative Medicine Treatment of Osteoarthritis

4.1 Introduction

Complementary and alternative medicine (CAM) is an umbrella term, defined variously as interventions neither taught widely in medical schools nor generally available in hospitals,(Astin, 1998, Eisenberg et al., 1998) or any intervention not usually prescribed by physicians,(Rao et al., 1999) or any treatment or therapy that is not generally available to patients by the National Health Service. (Maha and Shaw, 2007) It has also been defined as some medical preparations which can be bought over the counter without medical prescription.(Zochling et al., 2004) The National Center for Complementary and Alternative Medicine (NCCAM) in the United States defines it as "a group of diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine".(National Center for Complementary and Alternative Medicine, 2007)

In Australia, CAM has become a widely used form of healthcare. A series of surveys conducted in South Australia (MacLennan et al., 2006, MacLennan and Wilson, 1996, MacLennan et al., 2002) showed there had been an increase in the use of CAMs and CAM therapies between 1995 and 2006 which included herbal medicine, acupuncture, homeopathy, osteopathy, and naturopathy, and that over 50% of the representative survey population use CAM now. Educated, middle-aged women with higher incomes living in urban areas are the greatest users of CAM in many countries including Australia, United States and other developed countries.(Coulter and Willis, 2004, Eisenberg et al., 1998) Interestingly, a US study found the use of CAM in patients with musculoskeletal problems varies by racial or ethnic group: people with Asian backgrounds usually prefer herbal medicine and acupuncture, and African immigrants favour topical agents while Caucasians prefer to use dietary supplements.(Katz and Lee, 2007) There are complex reasons why people choose to use CAM, such as dissatisfaction with conventional medicine, a need of personal control of health, and people's belief in nature.(Eastwood, 2000) The percentage of Australians using various forms of CAM for osteoarthritis (OA) has been found to be around 40%.(Zochling et al., 2004)

CAM is increasingly being studied scientifically with respect to efficacy and safety, something that is necessary if CAM therapies are to have a place within national health systems. Much CAM research has been conducted within the field of rheumatology, an area of relevance given that many rheumatologic disorders have no known cure, are characterised by chronic pain and dysfunction, and conventional treatments are associated with undesirable side effects and substantial costs.(Rao et al., 1999) Glucosamine, chondroitin sulphate, and vitamin supplements are the most popular treatments for rheumatologic diseases.(Zochling et al., 2004) There are also some western herbal products widely accepted for symptomatic improvement of musculoskeletal pain management, like ginger, avocado-soybean and and devil's claw. This chapter will describe some of the major forms of CAM used to treat OA and the scientific evidence related to efficacy.

4.2 Nutritional supplements

4.2.1 Glucosamine

4.2.1.1 What is glucosamine?

Glucosamine is a natural substance that has been widely used as a food supplement to treat people with OA. It is an amino sugar that is synthesised from glucose and utilised for the biochemical synthesis of glycosylated proteins, lipids and glycosaminoglycan chains which produce aggrecan and other proteoglycans of cartilage.(Reginster et al., 2007) Glucosamine can be found in almost all human tissues, especially in the connective tissues like cartilage.(Dahmer and Schiller, 2008) OA is characterised as a progressive degradation and loss of articular cartilage which manifests as a disorder of increasing matrix structural protein turnover. Therefore it is believed that glucosamine may be beneficial for OA as the synthesis of aggrecan can enhance the hydrophilicity of cartilage.(Reginster et al., 2005) Glucosamine has been found in several forms and glucosamine sulphate is the most common commercial product, but there was a study showed glucosamine hydrochloride had a similar clinical efficacy to glucosamine sulphate.(Qiu et al., 2005)

4.2.1.2 The clinical trials of glucosamine and their findings

Since glucosamine is a precursor for glycosaminoglycans, and glycosaminoglycans are a major component of joint cartilage, supplemental glucosamine may help to

rebuild cartilage and treat arthritis. Glucosamine is commonly taken orally for the treatment of OA, but it can be used as an injection sometimes.(Towheed et al., 2005) Its use as a therapy for OA appears safe, but there is conflicting evidence as to its effectiveness. The evidence both for and against glucosamine's efficacy has led to debate among physicians about whether to recommend glucosamine treatment to their patients.(Manson and Rahman, 2004)

There were some clinical trials in the 1980s and 1990s that demonstrated benefits of glucosamine. However, it was argued that these studies were of poor quality due to methodological shortcomings, including small size, short duration, poor analysis of drop-outs, and unclear procedures for blinding.(Adams, 1999, McAlindon et al., 2000) Three large (at least 100 patients per group), placebo-controlled clinical trials of glucosamine sulphate have demonstrated a clear benefit for glucosamine treatment (Herrero-Beaumont et al., 2007, Pavelka et al., 2002, Reginster et al., 2001). There was not only an improvement in symptoms but also an improvement in joint space narrowing on radiographs. This suggested that glucosamine, unlike pain relievers such as NSAIDs, can actually help prevent the destruction of cartilage that is a distinctive characteristic of OA. But some smaller studies did not detect a significant benefit of glucosamine over placebo.(Cibere et al., 2004, Hughes and Carr, 2002)

Because of these equivocal results, some reviews and meta-analyses have evaluated the efficacy of glucosamine. Richy and colleagues performed a meta-analysis of randomised controlled clinical trials and found evidence of efficacy for glucosamine according to several outcomes, including the WOMAC index, the Lequesne index, the VAS pain and the VAS for mobility assessments, as well as good tolerability.(Richy et al., 2003) Bruyere and colleagues' review of glucosamine and chondroitin sulphate for the treatment of knee and hip OA concluded that both products act as valuable symptomatic therapies for OA with some potential structure-modifying effects.(Bruyere and Reginster, 2007) In addition, a review conducted by Anderson and colleagues in 2005 (Anderson et al., 2005) summarised the effects of glucosamine on glucose metabolism in in-vitro studies, the effects of oral administration of large doses of glucosamine in animals and the effects of glucosamine supplementation with normal recommended dosages in humans. They concluded that glucosamine does not cause glucose intolerance and has no documented effects on glucose metabolism.(Anderson et al., 2005)

Therefore, currently the Osteoarthritis Research Society International (OARSI) is recommending glucosamine as one of the eight evidence-based effective pharmacologic treatments for OA.(Zhang et al., 2008b) Likewise, the European League Against Rheumatism (EULAR) Practice Guidelines for Knee Osteoarthritis recommends glucosamine sulphate as one of the most effective treatment measure and accords it with the highest level of evidence.(Jordan et al., 2003)

4.2.2 Chondroitin sulphate

4.2.2.1 What is chondroitin sulphate?

Chondroitin sulphate is a glycosaminoglycan composed of a chain of alternating sugars usually found attached to proteins as part of a proteoglycan. Proteoglycan is an important structural component of cartilage and provides much of its resistance to compression.(Baeurle et al., 2009) Chondroitin's functions largely depend on the properties of the overall proteoglycan of which it is a part. These functions can be broadly divided into structural and regulatory roles. However, this division is not absolute and some proteoglycans have both structural and regulatory roles.

As part of aggrecan (namely large proteoglycan molecules), chondroitin sulphate is a major component of cartilage. The tightly packed and highly charged sulphate groups of chondroitin sulphate generate electrostatic repulsion that provides much of the resistance of cartilage to compression by increasing the synthesis of proteoglycans and thus their inhibition of interleukin 1β (IL-1β) in the cartilaginous matrix, and by increasing the synthesis of hyaluronic acid.(Kato et al., 1995) Loss of chondroitin sulphate from the cartilage is a major cause of OA.

4.2.2.2 Clinical trials of chondroitin sulphate

In several prospective controlled studies, chondroitin sulphate had been found to decrease pain, improve functional disability, and reduce NSAID or acetaminophen consumption, and have good tolerability with an additional carry-over effect.(Bourgeois et al., 1998, Mazieres et al., 2001, Morreale et al., 1996, Uebelhart et al., 2004)

There was some controversy regarding trials of glucosamine and chondroitin preparations for OA symptoms which demonstrated moderate to large effects, but

quality issues and likely publication bias suggests that these effects have been exaggerated.(McAlindon et al., 2000) In order to provide more reliable information about chondroitin's usefulness in treating OA, the National Institutes of Health of the United States funded a study to test the effects of chondroitin and glucosamine on OA of the knee. This multicentre, placebo-controlled, double-blind, six month long trial found that glucosamine and chondroitin alone or in combination had no statistically significant effect on symptoms of OA in the overall group of OA patients.(Clegg et al., 2006) But this study also suggested that the combination of glucosamine and chondroitin sulphate may be effective in the subgroup of patients with moderate-to-severe knee pain, being significantly more effective than placebo ($p = 0.002$) based on the primary outcome variable. They found that 79.2% of patients had a 20% decrease in the WOMAC pain score at the end of follow-up assessment in the glucosamine and chondronitin sulphate combined treatment group, and that there were only 54% of patients in the placebo group who had a 20% decrease in the WOMAC pain score. In addition, this primary outcome of the combined treatment group was also 10% higher than the Celecoxib control group even though this did not reach statistical significance ($p = 0.06$).

Importantly, this study also showed an effective response to chondroitin sulphate treatment: chondroitin sulphate significantly decreasing joint swelling for the mild knee pain subgroup from baseline to the end of follow-up (27.8% patients at baseline versus 11.7% patients at follow-up, $p = 0.02$). The percentage of all patients including the mild pain subgroup and the moderate-to-severe pain subgroup with signs of synovitis decreased from 28.3% at baseline to 12.4% ($p=0.01$, $n=307$) at the end of 24 weeks of treatment. In patients with moderate to severe pain (WOMAC pain scores 301 – 400), the percent of patients with swelling and/or effusion decreased from 30.0% at baseline to 14.9% ($p=0.3$, $n=67$) at the end of treatment.

Another 24-week, randomised, double-blind placebo-controlled study of chondroitin sulphate (1g/day) in patients with symptomatic knee OA as measured using a VAS and the Lequesne's index, failed to demonstrate significant efficacy of chondroitin sulphate for pain associated with daily activities, even though chondroitin sulphate was slightly more effective than placebo for pain management, physician global assessment and quality of life.(Mazieres et al., 2007)

Clinical studies have not identified any significant side effects or overdoses of chondroitin sulphate, which may support its long-term safety.(Hathcock and Shao, 2007) The Task Force of the European League Against Rheumatism (EULAR) Committee recently granted chondroitin sulphate a level of toxicity of 6 in a 0-100 scale, confirming it is one of the safest drugs for OA.(Jordan et al., 2003) Moreover, its safety is supported by an absence of reported drug-drug interactions, suggesting it is suitable for patients with OA who may be taking medications for co-morbidities, such as diabetes, hypertension, or hyperlipidemia.

4.2.3 Avocado-soybean oil

Avocado-soybean mixture, widely available in Europe, is made up of unsaponifiable fractions of one-third avocado oil and two-third soybean oil after hydrolysis.(Ameye and Chee, 2006) In- vitro experiments have shown that avocado-soybean unsaponifiable (ASU) stimulates aggrecan production and may have structure-modifying effects in OA by inhibiting cartilage degradation and promoting cartilage repair. (Henrotin et al., 2003) It has also been shown to affect monocyte/macrophage-like cells that serve as a prototype for macrophages in the synovial membrane leading to the pain-reducing and anti-inflammatory effects. (Au et al., 2007) Clinical evidence from three available well-designed and conducted trials (Appelboom et al., 2001, Lequesne et al., 2002, Maheu et al., 1998) has indicated that ASU, typically at a dosage of 300 mg once a day, is able to reduce pain and NSAID consumption.

Maheu and colleagues (Maheu et al., 1998) assigned 164 patients with OA of the hip and knee (classified as Kellgren-Lawrence grade 1-3) into two groups receiving ASU or placebo for 6 months, with 2 months follow-up. The primary outcome variable was the change of Lequesne's functional index. A significant reduction was observed in the ASU group at month 6 by intra-group and inter-group analysis. Similar results were also seen in the secondary outcomes including pain and functional disability on VAS, NSAIDs (or analgesic) consumption, and patient's overall assessment. In addition, improvements appeared to be more marked in patients with OA of the hip at two month follow-up after treatment discontinuation, suggesting that ASU seemed to have a delayed onset of action. A similar finding has been demonstrated in a three month, double- blind, placebo controlled trial conducted by Blotman and colleagues in 1997 as well.(Ernst, 2003)

In order to investigate the hypothesised structure-modifying effect of ASU, Lequesne and colleagues adopted the joint space width (JSW) as the primary assessment criterion in a two year placebo controlled trial of hip OA.(Lequesne et al., 2002) This study failed to demonstrate a structural effect of ASU though it there was a significant reduction in the progression of joint space narrowing in a subpopulation of more severely affected patients. In contrast, Appelboom and colleagues (Appelboom et al., 2001) randomised 260 patients with OA of the knee into three groups for three months treatment: a high dose ASU group, a low dose ASU group and a placebo group. They found that the high ASU dose (600mg per day) did not lead to superior results compared with the low dose (300mg per day) as assessed by the intake of NSAIDs and analgesics at baseline and the end of the trial, but there were significant improvements in all efficacy parameters ($p < 0.01$) comparing the two ASU groups to the placebo group.

However, there is a concern that all three trials used ASU from the one source and were industry funded, introducing the potential for bias.(Appelboom et al., 2001, Lequesne et al., 2002, Maheu et al., 1998) Based on the available evidence, a meta-analysis suggested that ASU is no worse and no better for the treatment of OA than other NSAIDs.(Christensen et al., 2008) Furthermore, there is also no evidence of significant adverse effects of ASU.(Christensen et al., 2008)

4.2.4 Green-lipped mussel

Green-lipped mussel (GLM) has been used as a health supplement since the 1970s based on the observation that Maoris who lived in coastal areas of New Zealand and consumed GLM regularly suffered less arthritis than their inland peers.(Brien et al., 2008) The encapsulated, freeze-dried GLM powder has been commerically promoted as an anti-inflammatory agent. Due to rapid oxidation, the potency of freeze-dried powder was more unstable and weaker than the supercritical lipid extraction from the mussel powder.(Whitehouse et al., 1997) However, a study (Gibson and Gibson, 1998) indicated there was no difference in either the efficacy or the speed of action between the lipid extract and the stablised GLM powder (which added 3% tartaric acid immediately after removing the flesh from the shell) in RA and OA patients.

The evidence of efficacy of GLM is variable amongst different studies. A systematic review (Brien et al., 2008) showed GLM was generally used as a complementary

treatment in OA in those published studies rather than as a cure or as a replacement therapy. No serious adverse events were found in those trials. But there were variations in the use of different preparations, manufacturers and dosing schedules. The positive or negative results may have been influenced by the concomitant use of NSAIDs or other factors. In addition, most clinical trials reported in two systematic reviews (Brien et al., 2008, Cobb and Ernst, 2006) which investigated the anti-inflammatory effect of GLM included combined data from RA and OA patients. Further studies specifically in OA patients are needed in order to establish the efficacy of GLM in the treatment of OA.

Animal experiements did not demonstrate similar outcomes either. It was reported that extracts of GLM failed to show anti-inflammatory activity in rats but showed positive alleviation in dogs' arthritis.(Cobb and Ernst, 2006)

It is believed that GLM may contain pharmacologically active inhibitors of prostaglandin biosynthesis which compete against the cyclooxygenase enzyme (COX; synthesis of prostaglandins) and the lipoxygenase enzyme (synthesis of leukotrienes). (Cobb and Ernst, 2006) The anti-inflammatory compounds in GLM is associated with the contents of the long chain omega-3 polyunsaturated fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).(Doggrell 2011) The mechanisms of omega-3 fatty acids in the anti-inflammatory action may rely on the selective blockage of the COX-2 pathway rather than the COX-1 pathway.(Cobb and Ernst, 2006) There is quite strong evidence of an assistant effect of fish oil in RA treatments but weak efficacy in OA. (Goldberg and Katz, 2007, Calder, 2006) However OA is not only associated with inflammatory changes. More studies need to be completed to understand the real mechanism of GLM in comparison with fish oil or EPA or DHA.

4.2.5 Others

There are also some other CAMs which may be of benefit for OA treatment, such as SAM-e (S-Adenosyl methionine). This nutrient is made from the amino acid methionine and ATP (Adenosine triphosphate). Some studies have suggested that SAM-e possesses anti-inflammatory and tissue-healing properties, incorporating sulfate groups into proteoglycans to help maintain the cartilage; this may protect the health of joints and perhaps may lessen pain.(Soeken et al., 2002, Ringdahl and Pandit, 2011) However, more studies are needed to verify this.

4.3 Vitamin and mineral supplements

4.3.1 Use of vitamin and mineral supplements for osteoarthritis

Many patients often use diet changes and/or vitamin and mineral supplements to help control pain and symptoms of rheumatic diseases, as a way of doing something to help themselves. Vitamin A, C and E are the major antioxidants in the diet and dietary supplements that have been identified as having important roles in preventing and/or improving oxidative stress caused by reactive oxygen species (ROS), part of the pathological processes associated with OA.(Rayman and Pattison, 2008, Sowers and Lachance, 1999) OA has been regarded primarily as a disorder of articular cartilage, but its other processes also play important roles in the pathophysiology of this condition, such as subchondral bone or subchondral sclerosis, and osteophytosis formation.(Iannone and Lapadula, 2003) Once cartilage damage is initiated, the stiffness of the subchondral bone may contribute to further progression and chondrocyte dysfunction.

Vitamin D also plays a role, stimulating the synthesis of proteoglycan by articular chondrocytes, influencing bone mineralisation and calcium metabolism.(McAlindon and Felson, 1997) In addition, evidence from both animal and human studies suggest that minerals including magnesium, copper, manganese, selenium and zinc have anti-inflammatory effects.(Henrotin et al., 2005, King et al., 2005, Kurz et al., 2002, Shakibaei et al., 1996)

Nonetheless the pathogenic mechanisms underlying the development of OA are not yet fully understood. It is believed there are at least four possible pathways in which these nutrients can influence OA: protecting against oxidative damage by free radicals; modulating immune responses of inflammation; regulating cellular differentiation; and forming structural components in the synthesis of bone and collagen.(Sowers and Lachance, 1999) Several clinical studies of the effectiveness of different vitamins and mineral supplements in the treatment of OA have been conducted in order to find if they are safer and more effective than non-steroidal anti-inflammatory drugs (NSAIDs) or other drugs that are associated with adverse effects during long-term use in OA patients.

4.3.2 Clinical trials of vitamins and mineral supplements

Research into the use of vitamins in the treatment of OA has mainly focussed on the degeneration of articular cartilage and the thickening of subchondral bone and the expression of antioxidative enzymes. Therefore, joint space narrowing (JSN), cartilage volume and serum vitamin levels have typically been used as outcome variables in clinical studies.

Vitamin A

Vitamin A has two forms naturally, one which is fat-soluble retinol generally derived from animal tissue, and another is a water-soluble pro-vitamin A (also known as beta-carotene) derived from plants and converted into retinol by the liver. Although vitamin A is necessary for growth and development of bone and soft tissue based on its effect on protein synthesis and bone cell differentiation, there is no unequivocal proof that vitamin A or supplementary retinol or beta-carotene can prohibit the initiation or progression of OA.(Sowers and Lachance, 1999) One study showed there was no significant difference in serum retinol values between OA patients and a normal matched control group ($p<0.3$), and a correlation among the serum osteocalcin, retinol and retinol binding protein in OA patients was not demonstrated even though the mean serum osteocalcin was higher than normal in OA.(Fairney et al., 1988)

Vitamin C

Vitamin C, ascorbic acid, cannot be synthesised by human bodies and must be obtained from dietary sources. It is believed that ROS which are produced in normal metabolism or inflammatory mechanisms can lead to some age-related diseases, and that ROS can also be generated by both chondrocytes and neutrophils at joint sites and cause damage to hyaluronate and the components of cartilage matrix such as proteoglycans and collagen.(Tiku et al., 2000, Yudoh et al., 2005) A subgroup study of the Framingham Osteoarthritis Cohort Study (McAlindon et al., 1996b) indicated that moderate to high antioxidant intake, especially vitamin C, could reduce the risk of cartilage loss and so protect against OA progression based on the outcomes of osteophytosis and joint space narrowing, but there was not enough evidence to support the contention that increased intake of antioxidant nutrients could reduce the incidence of knee OA. However, a systematic review did not find convincing

evidence of clinical efficacy in the treatment of OA by antioxidant vitamins A, C, or E.(Canter et al., 2007)

Vitamin D

Vitamin D, a compound derived largely from the diet or from cutaneous exposure to ultraviolet light, is probably the most controversial vitamin in the treatment of OA. Because normal bone metabolism depends on the presence of vitamin D, insufficiency of vitamin D may have adverse effects on calcium metabolism, osteoblastic activity, matrix ossification and bone density.(Grant, 2006, Parfitt et al., 1982) A study investigating the association between the serum levels of vitamin D, sunlight exposure and knee cartilage volume assessed by radiograph and magnetic resonance imaging (MRI) showed serum levels of 25-hydroxyvitamin D were significantly associated with moderate-to-severe JSN of knees, and that insufficiency of vitamin D also influenced loss of cartilage volume.(Ding et al., 2009) This study did not, however, find a significant association between vitamin D insufficiency and knee cartilage defects. The study also indicated that the sunlight effect on cartilage volume was still debatable even though there was some evidence which showed less knee cartilage loss amongst patients who had more sunlight exposure, since this might be due to increased physical activities during sunlight exposure rather than the sunlight itself.

Another observational study suggested that the patients with low intake of vitamin D and low serum levels of 25-hydroxyvitamin D were associated with an increased risk of progression of existing knee OA but there was no evidence to support the contention that insufficiency of vitamin D would increase the risk of developing OA in a normal knee.(McAlindon et al., 1996a) This study mainly replied on radiographic signs, a self-administrated food frequency questionnaire and blood samples as methods of assessment. Interestingly, another epidemiologic study from the same research team on the offspring of the previous cohort and another cohort found no association between vitamin D levels and increased structural damage in existing knee OA as measured by JSN (using radiography) and by cartilage loss scores on MRI.(Felson et al., 2007)

In addition, a study that investigated altered bone turnover, vitamin D and calcium regulation with knee OA in female twins did not support findings of other studies that the level of serum vitamin D increased the risk of OA (which the authors point out

may have been due to investigators not adjusting for the confounders age and body mass index).(Hunter et al., 2003) However this study indicated bone resorption was increased in women with knee OA as manifested by urinary deoxypridinoline (DPD), which was consistent with metabolically active subchondral bone expressed as bone turnover in OA.

A recent large scale study (1248 subjects) demonstrated that improving the vitamin D status in the elderly could protect against the development and worsening of knee OA, especially in those with low bone mineral density (BMD).(Bergink et al., 2009) The effectiveness of vitamin D in the treatment of OA is still in need of further research.

Vitamin K

Vitamin K is an important regulator of bone and cartilage mineralisation, and is usually concentrated in green leafy vegetables in the form of phylloquinone.(Booth and Suttie, 1998) Results of a study supported a significant association ($p \leq 0.03$) between low plasma levels of vitamin K and the increased presence of large osteophytes in both the hand and knee, but there was only a significant link between the phylloquinone level and JSN in hand OA but not in the knee OA.(Neogi et al., 2006) In addition, the researchers admitted that it is difficult to distinguish nutrient effects from effects of a healthy lifestyle, therefore, they recommended that caution should be exercised in interpreting the results.(Neogi et al., 2006)

Minerals

As for mineral research in musculoskeletal diseases, most studies have focused on rheumatoid arthritis (RA) rather than OA. Current research data suggests that copper, zinc and iron should be taken in adequate amounts from diet in order to reduce joint inflammation, but the results have been contradictory.(Rayman and Pattison, 2008) A small sample trial indicated that a multi mineral supplement derived from seaweed (Aquamin) was associated with a significant reduction in the WOMAC pain score similar to glucosamine sulphate,(Frestedt et al., 2008) but this study was only of short duration (12 weeks treatment) and no follow-up was conducted post-cessation of treatment. These results should be verified by further research. In addition, an animal study in STR/1N mice with mechanically induced OA found that a diet supplement (vitamins and selenium) could lead to decreased degeneration grading of OA lesions

of articular cartilage as evaluated histologically, which might be due to the increased expression of antioxidative enzymes.(Kurz et al., 2002)

4.4 Western herbal medicine

Despite wide use of physiotherapy and NSAIDs, there is a great interest in non-synthetic, natural medicines derived from herbal sources for the treatment of OA. Many herbal remedies, based on plants or their extracts, are used for the treatment of arthritis and OA. Herbalism is diverse and includes that derived from Greek and Roman sources, the Siddha and Ayurvedic medicine systems from various South-Asian Countries, Chinese herbal medicine, and other forms of herbalism from South America and Africa.(WHO, 2008)

Whilst the gold standard for testing of pharmaceutical drugs is large scale, double blind, randomised controlled trials, many of the studies into herbal medicines have been conducted on a smaller scale. Though there have been positive results demonstrated within in-vitro or small-scale clinical research into herbal remedies, the quality of the studies is highly variable and many have been of poor quality.(Linde et al., 2001) Some of the more popular western herbs and derivatives include ginger extract, avocado-soybean, rose hip, Rosa Canina (cat's claw), comfrey root, and Boswellia Serrata. One of the main differences between western herbalism and Chinese herbal medicine is that in Chinese medicine, single herbs are rarely used.

4.4.1 Ginger extract

Ginger is the rootstock of a very popular spice *Zingiber officinale*, with a long tradition of medical use in Ayurvedic and Chinese medicine.(Ali et al., 2008) Ginger has a complex mixture of compounds and the available ginger extracts for OA treatment are mainly EV.EXT-33 (Eurovita Extract 33) and EV.EXT-77 (combined extracts of *Zingiber officinale* and *Alpinia galangal*).(Chrubasik et al., 2005)

A six-week, double-blind, placebo controlled, parallel group trial (Altman and Marcussen, 2001) assessed the efficacy of a concentrated extract (EV.EXT-77) of dried ginger rhizomes and dried galangal rhizomes in the treatment of 247 patients with knee OA grade 2-4 severity according to the Kellgren-Lawrence X-ray ranking system. The results indicated there was a higher rate of responders in the EV.EXT-77 group than in the placebo group ($p=0.04$) on the WOMAC VAS pain scale. In

addition, the greatest improvement in the WOMAC index analysis in patients who received the ginger extract was seen in stiffness rather than pain. In this short-term study, there was no significant difference in the ginger extract and placebo groups in the quality of life (measured by the SF-12) and consumption of acetaminophen ('rescue medication'). But there were significantly more gastrointestinal (GI) adverse events in the ginger extract group compared with the placebo group, though none of these were considered serious by the investigators.

A cross-over study randomised 75 patients with OA of the hip or knee and radiological ranking of grade 1-4 on the Kellgren-Lawrence scale.(Bliddal et al., 2000) Each patient received three treatment phases of three weeks each with either, 170mg EV.EXT-33, Ibuprofen 400mg or placebo. There was no washout period applied between the three treatment periods except for one week washout before the trial. Acetaminophen was allowed as a rescue medication. This study demonstrated that Ibuprofen was more effective than ginger extract and placebo on pain assessment (as measured on a 100 mm VAS) and global function (Lequesne Index). The same finding was also seen in the consumption of rescue medication, that less acetaminophen were taken in the Ibuprofen group than in the ginger extract group and placebo group ($p < 0.01$). However, the treatment period of this study may be too short to fully investigate the change in patients' conditions.

The current studies of ginger extract have not reached a consistent conclusion. Another cross-over trial compared enteric coated ginger extract and placebo in 29 knee OA patients (of Kellgren-Lawrence grade 2-4), each for a 12 week treatment period.(Wigler et al., 2003) During the first 12 weeks (phase one), the difference between groups were not statistically significant though both groups showed a significant decrease in VAS measures of pain and handicap compared with the baseline. However in the second phase, the VAS scores of pain and handicap started to increase in the group who switched from ginger extract to placebo while the scores continued to decrease in the group who switched from placebo to the ginger extract. Furthermore, there was a significant difference between the two groups by the end of 24^{th} week. ($p<0.001$) This study suggests that ginger extract was effective in the treatment of OA. However, this study had a high drop-out rate (28% and 33%) and a small sample size and there was no wash-out period between the two phases, opening the study to criticism. Therefore, the attitude towards ginger extract for OA treatment

in mainstream medicine is still guarded, as it is thought research studies conducted have not met the same standards for efficacy and safety as conventional therapies.(Marcus and Suarez-Almazor, 2001)

4.4.2 Rose hip

Rose hip is the fruit of the rose plant, and certain species, especially Rosa canina, have been used as herbal remedies in the Scandinavian countries. The dried powder of rose hip (Rosa canina) made from the fruit including its seeds and the shells, has been found to reduce chemotaxis of peripheral blood neutrophils and monocytes of healthy subjects in- vitro, and reduce serum C-reactive protein (CRP) levels for healthy volunteers and patients suffering from OA following treatment for 4 weeks.(Winther et al., 1999)

A three month, placebo-controlled, cross-over RCT (Winther et al., 2005) of patients with hip or knee OA found that the WOMAC pain score was significantly reduced in the rose hip group after three weeks treatment compared to placebo group, but there was no significant difference after three months treatment. This result was explained as being consistent with a significant decline in consumption of rescue pain killers after the first three weeks in the rose hip group. On the other hand, the stiffness score and physical activities score of the WOMAC and patients' global assessment were significantly decreased (improved) compared with placebo after three months treatment (though they were not statistically different at the end of the first three weeks).(Winther et al., 2005). The study also suggested there was a carry-over effect of rose hip powder and its anti-inflammatory action which was not due to its high vitamin C content.(Winther et al., 2005)

The carry-over effect of the powder of Rosa canina fruit was also demonstrated by another three month, cross-over, placebo-controlled RCT.(Rein et al., 2004) The study utilised five-point Likert-scale questionnaires of pain and stiffness as well consumption of rescue medications.(Rein et al., 2004) Group A (placebo first) showed significant difference between the real medicine and placebo in terms of the severity of joint pain and stiffness, and the consumption of concomitant pain-relieving medicine whilst Group B (rose hip first) did not show a significant difference. The study could be criticised for inclusion of patients with OA of various joints instead of confining it to a single joint, given that OA of the hand, hip, knee, neck and shoulder

have different impacts on patients' daily lives which may influenced subjective assessments and the in-take of rescue medication.

4.4.3 Cat's claw

Cat's claw is a thick woody vine from the basin of the Amazon rainforest. The bark of the vine has been traditionally prepared as a decoction and drunk as a tea for the treatment of chronic inflammation in South America for over 2000 years.(Erowele and Kalejaiye, 2009) There are two most commonly used species of Cat's claw, Uncaria tomentosa and Uncaria guianensis. The active chemical constituents from its bark include quinovic acid glycosides, sterols, oxidole and alkaloids contents.(Hardin, 2007) Although Cat's claw is classified as the same family (Rubiaceae) and genus (Uncaria) as a Chinese herb, Gou Teng (Uncaria rhynchophylla), they are different in the chemical constitutions and medicinal uses. (Heitzman et al., 2005)

The antioxidant and anti-inflammatory properties of its water-soluble extracts are believed to be due to a cytoprotective action against peroxynitrite, thereby preventing the side effects of NSAIDs on the intestine.(Sandoval-Chacón et al., 1998) At the same time the extract of Cat's claw is an effective inhibitor of inducible nitric oxide synthase gene expression, suppressing the activation of the transcription factor NF-$_K$B.(Sandoval-Chacón et al., 1998) A further experiment indicated the primary mechanism of Cat's claw anti-inflammatory actions is immunomodulation by suppression of TNF-α synthesis.(Sandoval et al., 2000)

A placebo-controlled, parallel-design RCT (Piscoya et al., 2001) targeting male patients with knee OA found the Cat's claw group had a significant improvement in the score of pain on activity (measured by a four-point scale), patients' global assessment and physicians' global assessment compared to placebo, but there were no significant change in the score of pain at rest and knee circumference in either group. However, caution needs to be taken with respect to the findings of this study. Firstly, the study involved small numbers (30 subjects in the Cat's claw group, 15 in placebo group) and was of short duration (four weeks). Secondly, there was no information about the number of drop-out patients and no follow-up assessment. Thirdly, the evaluation of knee pain was mainly based on the physicians' examinations plus patient's subjective sensations. Further large scale studies are clearly needed in order to reach a definitive conclusion regarding efficacy of Cat's claw.

4.4.4 Indian frankincense

Indian Frankincense (Boswellia serrata) is the gum resin from the Boswellia tree grown widely in hilly areas of Northwest India. It has been used as an anti-inflammatory and analgesic drug in Ayuredic medicine.(Basch et al., 2004) It is categorised as the same genus as Boswellia sacra in the Burseraceae family, but the aroma of Boswellia serrata is generally considered to be far inferior compared to Boswellia sacra (as the Chinese herb Ru Xiang). Ru Xiang is used for the treatment of rheumatism, menstrual pain and bruises traditionally in CM.(Basch et al., 2004, Wikipedia) Boswellic acids are the most active component of Boswellia extracts and the major ingredients of Boswellia species, and are potent inhibitors of 5-lipoxygenase, a key enzyme in the cellular inflammatory cascade.(Poeckel and Werz, 2006)

A cross-over, placebo-controlled RCT of Boswellia sacra extracts (Kimmatkar et al., 2003) in patients with knee OA assessed pain, function and swelling on four-point, Likert-like scales. At the end of the first treatment phase (8 weeks), there was a significant decrease in scores relating to pain, function and swelling in the treatment group compared with placebo ($p<0.001$). After 21 days washout at the end of first treatment period and crossover, scores in those in the placebo group kept relatively stable whilst scores in the treatment group continued to decrease. Boswellia sacra extracts were also well tolerated by the patients except for minor gastrointestinal adverse events. However, there was no change of radiograph signs of the affected knee joint. Another placebo-controlled study (Sengupta et al., 2008) evaluated the clinical efficacy of two different dosages of Boswellia sacra extract, using the WOMAC index visual analogue scale (VAS) and the concentration of matrix metalloproteinase-3 (MMP-3) in synovial fluids of knee joint as the outcome variables. The trial found both dosages of Boswellia sacra extracts significantly reduced the WOMAC pain scores and physical activity scores in OA patients at the end of three months treatment compared with baseline and with the placebo group, and that the MMP-3 concentration had been significantly reduced in the treatment group compared with the placebo group. As for any differences between the high-dose group and low-dose group, differences were observed only for the pain VAS and MMP-3 concentration. This trial was funded by the medicine provider and there was no follow-up assessment. In addition, Boswellia sacra has also been used in the

compound of Ayurvedic herbs for OA treatment and preliminary results have demonstrated its potential positive efficacy.(Chopra et al., 2004) Further investigations are needed to establish therapeutic efficacy and safety.

4.4.5 External application of herbs

There are also some herbs which have been applied externally for OA treatment as phytopharmaceutical drugs or homeopathic treatment in Europe. One study showed that 21 days of treatment with comfrey root liquid extract ointment could reduce pain, improve the mobility of the knee and increase the quality of life compared with placebo, as assessed by the WOMAC Index and SF-36 questionnaire respectively.(Grube et al., 2007) There were no reports of serious adverse events associated with this ointment.(Grube et al., 2007) A homeopathic gel which also contains comfrey (Symphytum officinale) has been found to be at least as effective and well-tolerated as the NSAID gel in patients with knee OA after four weeks treatment.(van Haselen and Fisher, 2000) These studies do not provide unequivocal evidence of efficacy and safety of comfrey, however, since they are relatively short in duration and there were difficulties with blinding.(van Haselen and Fisher, 2000) Longer term, rigorous studies are still needed.

4.5 Conclusion

The use of CAM for the treatment of OA has become an important issue for rheumatologists. The data summarised above shows that rigorous trials of CAM have been conducted and there is a growing evidence base to support efficacy of some forms of CAM in the treatment of OA. However, there are concerns regarding the methodological quality of some studies.

Glucosamine and chondroitin are the most studied products amongst these complementary medicines and both have been accepted as safe and effective in comparison to placebo, particularly in certain sub-populations. Although vitamins or mineral supplements are quite popular amongst OA patients, evidence of their clinical efficacy is equivocal. Current research mainly focuses on the links between their anti-oxidant properties and the impact on degeneration of articular cartilage. As for western herbs, the evidence to date in support of clinical efficacy is not convincing though some studies have claimed positive findings. Further large scale trials are

required, not only to establish efficacy but also the safety of complementary medicines.

Unlike western herbalism, CM seldom uses single herbs: rather, several herbs are combined in a medicinal formula as described in Chapter 8. Chinese herbal medicine (CHM) formulae target not only the ‘root’ causes of illness but also the symptoms and signs (as described in Chapter 2). Different CHM formulae may be offered at different stages of OA. Combinations of herbs may be chosen to specifically address a particular CM Syndrome or combination of Syndromes, and in accordance with particular theories utilized by the practitioner. The next chapter will discuss how Chinese medicine understands and treats OA.

Chapter 5 Chinese Medicine Understanding of Osteoarthritis

5.1 Introduction

The term ‘osteoarthritis’ (OA) did not exist in ancient Chinese medical books, but there were many descriptions of diseases which had similar clinical characteristics to OA. In Chinese medicine (CM), it is generally believed that OA should be categorised as ‘Bi syndrome’, specifically ‘Bi syndrome of bone’. The word ‘Bi’ means painful obstruction which may manifest as symptoms including as pain, numbness, paralysis, lack of sensation and stiffness. Furthermore, in a broader sense the concept of ‘Bi’ also includes painful obstruction within organs which could be seen as referring to the possible complications of rheumatism.(Guillaume and Chieu, 1996) In the two official clinical guidelines of People's Republic of China (*Criteria of Diagnosis and Therapeutic Effect of Disease and Syndromes in Traditional Chinese Medicine; Clinic Terminology of Traditional Chinese Medical Diagnosis and Treatment - Syndromes*), OA and degenerative arthrosis are both called as Bi syndrome of bone.(China State Administration of Traditional Chinese Medicine, 1994, China State Bureau of Technical Supervision, 1997)

5.2 Aetiology and pathogenesis of osteoarthritis

As described previously, according to CM the causes of diseases include six exogenous factors; the seven emotions, improper diet, overstrain and lack of physical exercise, trauma, insect bites and stagnation of Blood and Phlegm or Fluids.(Aung and Chen, 2006) The pathogenesis of Bi syndrome involves obstruction of exogenous Wind, Cold and Dampness, or Heat in the body where there is an underlying deficiency of ‘Upright’ or ‘Zheng’ Qi (the primary Qi of the body). In the majority of cases, the external causes of Bi Syndrome are a combination of three pathogens: Wind, Cold and Dampness.(Zhang et al., 1985)

Symptoms of Bi Syndrome are pain in the muscles, sinews or joints, stiffness or disability of the joint, and in some cases swelling of the joint due to blockage of the meridians and impeded Qi and Blood circulation.(Zhang et al., 1985) Pain is the main symptom, typically with joint use, and also stiffness of less than 30 minutes duration.(White, 2006) Mild cases of Bi Syndrome result in pain in the limbs and joints that may become more pronounced with changes in the weather; in severe cases

there is greater soreness and pain, deformities and decreased range of movement.(Aung and Chen, 2006) In general, OA is in accordance with the features of Bi syndrome, though some patients with pathologic and radiographic evidence of OA have no symptoms.(Felson et al., 2000)

However, degenerative rheumatic diseases like OA and inflammatory rheumatic disease such as rheumatoid arthritis, can both be described as Bi Syndrome. In other words, there is not a direct one-to-one correspondence between OA and Bi Syndrome.

According to CM, local pathological changes of OA are closely linked to the internal (Zang-Fu) organs through the meridians and the circulation of Qi and Blood. This example exemplifies the differences between CM and western medicine. CM does not analyse pathological changes at the microscopic level, for example via changes in blood chemistry. It is primarily concerned with the broad disease process and in understanding the relationships amongst the various pathogenic factors, the circulation of the Blood and Qi and harmony of the Yin and Yang organs. Internal causes of Bi Syndrome are emphasised in the disease process of OA.

OA is regarded as a syndrome where the root or 'ben' is 'deficient' and the symptoms/manifestations or branch ('biao') is 'full' (excess). Weakness of the person's constitution is the foundation for the occurrence of the disease. Ageing is a natural process, characterised by the decline of the body's Essence or Jing, the substance that forms bones and is responsible for growth and development and basic constitutional strength. With age, the internal organs age, their energy (Qi) becomes depleted, the bone and tendons become frail and stiff, and movement is hampered.(Ni, 1995) A deficiency condition - deficiency of the body's Zheng Qi - is the basis of Bi syndrome. As explained in Chapter 2, a deficiency condition is always related to the five internal Zang Organs. It is generally believed that the Kidney is the primary organ in the development of Bi syndrome, and the Liver is the secondary factor.(Jiang et al., 2001) The Kidney Essence (Jing) nourishes and 'controls' bones through marrow which is itself produced by the Kidney-Essence. Osteophytes are characteristic of OA, and the bones are related to the Kidneys according to CM.(Du et al., 2002) The Liver stores Blood and 'controls the sinews' (which include tendons, cartilages and ligaments of the limbs) via the nourishing and moistening functions of Blood. The decline of Kidney-Essence and deficiency of Liver-Blood as a result of

aging constitute the foundation of OA. In addition, the Spleen is also involved in the pathogenesis of OA. It controls and nourishes the muscles and the limbs by transforming and transporting food essence (‘Gu Qi’) and fluids. Spleen deficiency may cause the formation of internal Phlegm (a type of condensed body fluid) which can further condense to form bone growths (osteophytes). Phlegm also can impede the function of the Spleen in producing Blood from foods, thereby failing to reinforce or replenish Kidney-Essence and Liver-Blood, leading to a deficiency of Kidney Essence and Liver Blood. Moreover, the Spleen is also easily affected by external Dampness,(Maciocia, 2005) one of the main exogenous pathogenic factors involved in the pathogenesis of Bi Syndrome.

With an underlying weakness of the Zheng Qi, the combination of three exogenous pathogens, Wind, Cold and Dampness, readily invade the body and block the flow of Qi and Blood. The pathogens accumulate in the meridians and around the joints. This blockage leads to pain, the main symptom of Bi Syndrome. In addition, Blood stasis and (non-substantial) Phlegm are pathological metabolites of Bi Syndrome caused by blockage, which conversely can become aetiological factors. When the flow of Qi and Blood is impeded and Body Fluids cannot be transformed and accumulate in the joints over a long period of time, this can subsequently lead to deterioration of the OA.(Xiao, 2004)

5.3 Arguments about identification of Syndromes of osteoarthritis

Although OA has generally been equated with Bi Syndrome, there have been arguments with respect to the classification of OA over the past few decades. A key factor in classifying OA as Bi Syndrome is the fact that pain is a major feature of the disease. However, the pathogenic changes of OA occur in articular cartilage and tissue around the joint which are classified as belonging to ‘sinews’ in CM, and the sinews are considered to be an extension of the Liver. The knees are also understood to be ‘the palace of the tendons’.(Ni, 1995) If one cannot bend or straighten a joint properly or one needs to overcompensate in order to move, it is indicative of impending tendon degeneration.(Ni, 1995) Therefore, it has been argued by some that OA should be categorised as a disease of the sinews.(Cao et al., 2006b) This is logical and can be explained in accordance with CM theory. If Liver-Blood is deficient, the sinews will lack moistening and nourishment, which may cause symptoms such as

contractions and spasms, impaired flexion, numbness of limbs, tingling and muscle cramps. If there is stasis of Liver-Blood, the sinews will lack suppleness and the person may experience stiffness, rigidity and pain of the joints.(Maciocia, 2005)

A new theory has emerged that places the emphasis on the Liver in the aetiology and pathogenesis of OA. It suggests that OA should be considered as a combined pattern of Bi Syndrome and Wei (Atony) Syndrome, with the fundamental disorder being Wei Syndrome and the secondary disorder being Bi Syndrome. Wei Syndrome is defined as a progressive weakening or degeneration of the limbs owing to Qi, Blood or Body Fluid and Essence deficiency, manifesting as flaccidity of the sinews or muscle and, in the end, loss of voluntary movement of the limbs.(Zhang et al., 1985) Professor Shi Yinyu of the Shanghai Shuguang Hospital (affiliated to the Shanghai University of Traditional Chinese Medicine) is a major proponent of this theory, and his clinical experience and success in treating patients according to this theory supports this notion.(Shi et al., 1994)

The argument that OA should be considered as a combination of Wei Syndrome and Bi Syndrome is not unreasonable and finds support within CM theory. Wei Syndrome is associated with deficiency of the internal organs. Symptoms and signs of OA in the initial stage are indicative of 'painful obstruction' (Bi Syndrome), however the clinical manifestation of advanced OA is an atrophy of muscles of the limbs (from lack of use), a major feature of Wei syndrome. The symptom of numbness is also common to both Bi Syndrome and Wei Syndrome. The Kidney Jing and Liver Blood are understood to have a common source. According to CM theory, by fifty-six years the Liver energy weakens causing the tendons to stiffen,(Ni, 1995) consistent with a key clinical feature of Wei Syndrome: atrophy. CM theory also says that the Kidney Qi begins to decline over the age of 40 years (Chapter 1 of the ancient medical text, the *Su Wen*).(Ni, 1995) The decline in functioning of the Liver and Kidney with age described in CM theory is in keeping with the epidemiology of OA: that approximately 40% of adults over 70 years old are affected by OA of knee, 80% of whom have limitations of movement and 25% of whom cannot perform major daily activities of living.(Crepaldi and Punzi, 2003) There are also obvious clinical signs and symptoms of Kidney deficiency among elderly people who are the majority patients suffering with OA. For these reasons, it has been argued by some that OA

should be considered a combination of Bi Syndrome and Wei Syndrome.(Cao et al., 2006b) This emerging theory has important consequences for the treatment of OA.

5.4 Treatment principles of osteoarthritis in Chinese medicine

As explained previously, OA has previously been classified a type of Bi Syndrome due to 'Deficiency of Kidney and Liver' and invasion of exogenous pathogenic factors causing obstruction of Qi and Blood circulation, leading to pain and dysfunction of joint and muscle. It logically follows that the treatment principles should emphasise tonifying (strengthening) the Kidney and Liver, nourishing Qi and Blood and expelling Wind-Cold, removing Dampness and where there is Qi and Blood stagnation, promoting Blood circulation and removing obstruction from the collaterals. These treatment principles have been accepted within CM and corresponding medicinal formula developed and applied on the basis of this. In addition, there are some medicinal formulae that place the emphasis on invigorating the Spleen when there is inflamed, degenerative joints,(Cao et al., 2006b) however this is usually for a particular stage in the pathological process and cannot be applied for all stages of the pathogenesis of OA. Acupuncture treatment likewise has followed these treatment principles. For example, it is said that when the skin and muscles are involved, shallow needle insertion is prescribed (since skin and muscle are considered to be at a relatively superficial level), but when bone and tendon Bi are involved, the needle should be inserted deeply and retained.(Aung and Chen, 2006) Treatment of OA by traditional Chinese therapeutic massage also focusses on removing obstructions in the channel pathways by promoting Qi and Blood circulation, reducing slight displacement of the joints or healing soft tissue injuries through applying manual methods.

In contrast, if OA is regarded as a combination of Wei Syndrome and Bi Syndrome, with Wei Syndrome being predominant, the therapeutic thrust shifts to nourishing the Liver, 'soothing the sinews', and eliminating exogenous pathogenic factors.(Cao et al., 2006b) Less emphasis is placed on the Kidney comparatively. Consequently, different kinds of herbs are used in medicinal formulae.

Animal experiments have lent support to this treatment principle in experiments. Comparing the thickness and density of knee cartilage amongst groups treated with different herbal formulae, it has been found that treatment methods that focussed on

nourishing and ‘soothing’ the Liver were associated with better histopathological results, particularly in synovitis (a complication of OA) than treatment methods in which the Liver was not treated.(Shen et al., 1995, Wang et al., 1998)

Ideally, strategies for treating OA should be comprehensive and should involve consideration of several treatment principles including nourishing and soothing the Liver, tonifying the Kidney, invigorating the Spleen, removing Blood stasis and resolving Phlegm, in addition to considering the broader issue of Wei Syndrome and/or Bi Syndrome.(Guo et al., 2002) Thus if the Liver is the key organ, Chinese herbal medicinal (CHM) formulae need to have a greater emphasis on nourishing the Liver Blood than on tonifying the Kidney, with pungent and drying herbs typically found in CHM formulae treating Bi Syndrome giving way to mild and nourishing herbs.(Liu, 1999, Shi et al., 1994)

5.5 Clinical treatment for osteoarthritis with Chinese medicine

5.5.1 Chinese herbal medicines

The majority of CHMs for the treatment of OA follow basic Syndrome identification, with an emphasis on tonifying the Kidney and Liver, promoting Blood circulation and expelling Wind and resolving Dampness.(Li, 2003a) There are some herbal formulae that place an emphasis on ‘invigorating’ the Spleen when there is an inflamed, degenerative joint. Typically, most CHM formulae focus specifically on a certain stage of the disease process, thereby addressing only part of the pathogenic process.(Kang et al., 2005)

Proprietary CHMs in the form of pills have been found to be the most common form of CHMs used for OA.(Liu et al., 2005a) Herbs with actions of ‘dispersing exogenous Wind and Dampness’, ‘tonifying blood’ and ‘activating Blood circulation’ were found in one survey to be the most common components of OA CHMs; over 50% of herbs in formulae were pungent, sweet and bitter in terms of taste and warm in terms of temperature characteristic. Mu Gua, Du Huo, Fang Feng, Gui Zhi and Wei Ling Xian were the most frequently used herbs for Expelling Wind and Dampness in formulae; Xu Duan, Gou Ji, Shu Di Huang, Ren Shen and Huang Qi were prescribed often as Tonifying herbs, and the most commonly prescribed herbs for Eliminating Blood stasis were Niu Xi, Chuan Xiong, Hong Hua, Ru Xiang and wine.(Liu et al., 2005a)

External use forms of CHM primarily address symptoms rather than underlying root causes (as internal CHM does).(Wu et al., 2006a) Fumigation-washing therapy, plaster or ointment applications and ionotherapy with CHM are the most common external therapies used in clinic. An investigation of 87 different external-use formulae for OA found that herbs with an action of dispelling Wind-Dampness and herbs that eliminated Blood stagnation were most commonly used and that 73% of the most commonly prescribed herbs were warm in nature.(Yao et al., 2005) In Chinese hospitals, intra-articular injection of CHMs into the knee cavity has been applied as a form of therapy,(Zhang et al., 2005c) however few studies have investigated its effectiveness and many have been methodologically flawed.(Wan et al., 2006)

5.5.2 Acupuncture

Acupuncture has been widely used for treatment of OA of the knee and chronic knee pain,(Kwon et al., 2006, White et al., 2007a) and, at least in China, commonly in conjunction with other techniques including electronic stimulation (electro-acupuncture),(Lao and Deng, 2003, Wu, 1998, Wu and Bao, 2008) moxibustion,(Bao et al., 2007) electronic heat lamps and other special electromagnetic therapeutic apparatus,(Cai and Huang, 2004, Lin and Liang, 2005, Wang and He, 2007) acupoint injection, cupping, physical exercise and herbal medicine (oral, external and/or ionotherapy methods).(Bao et al., 2007) The technique of ‘warming needling’ is the most popular treatment modality for OA (moxa is placed at the end of the needle after insertion, lit then allowed to smoulder,(Le, 2001, Li et al., 2006, Lin et al., 2004a, Wu et al., 2006b) in keeping with the idea that OA is due to Kidney deficiency and Cold and Dampness invasion and retention.(Yang et al., 2007a) Laser is also used for OA treatment in China.(Xi et al., 2008)

5.6 The scientific evidence base of Chinese medicine in OA treatment

Historically, in comparison with rheumatoid arthritis, OA has not been a priority research area.(Birrell, 2004) Studies of complementary and alternative medicine (CAM) have found that CAM is cost-effective and can reduce the burden of OA,(Herman et al., 2005) which was estimated as costing Australia AUD$1090 million in 2001.(Segal et al., 2004)

To understand the scientific evidence base for the treatment of OA with CM I conducted a literature search of clinical studies that investigated the efficacy of acupuncture and CHM in treating knee OA. The literature search used two key databases- the English language database PubMed (including Medline) and the large Chinese database www.cqvip.com were searched thoroughly during April 2007 to August 2007. Search terms used included: 'osteoarthritis', 'Chinese medicine', 'acupuncture', 'herbal medicine', 'RCT', 'knee' and 'double-blind'.

The Jadad Scale, a research tool used to assess quality of randomized controlled trials (RCTs) in pain research,(Jadad et al., 1996) was applied to the studies identified. The Jadad Scale has been found to be reliable in a number of different settings,(Clark et al., 1999, Moher and Fortin, 1996, Olivo et al., 2008) however like many scales used to assess methodological quality, it has limitations. For example, it is not particularly suitable for assessing studies of treatment interventions such as manual therapy or exercise therapies since double-blinding is unlikely to be a feature of such studies. There is no assessment tool specific for CAM research requirements.(Katrak et al., 2004)

A modified version of the CONSORT (Consolidated Standards of Reporting Trials) Statement was also applied to the studies (see Appendix 1 and Appendix 2). The CONSORT Scale was developed by a group of scientists, epidemiologists and editors to improve the quality of reporting of RCTSs and offer a standard way aiding the design, conduct, analysis, and critical appraisal and interpretation of trial findings. This 22-item checklist, first published in 1996 and revised in 2001,(Begg et al., 1996, Moher et al., 2001) has gained considerable support worldwide with one systematic review suggesting the use of the CONSORT was associated with improved reporting of randomised trials.(Plint et al., 2006) Several versions of the CONSORT Statement have been developed, including those for trials of herbal interventions and non-pharmacologic treatments. However one study has found that most CM journals in China do not include the CONSORT Statement in their instructions to authors and the quality of reporting of RCTs of CM is still poor.(Wang et al., 2007a)

5.6.1 Results of Chinese herbal medicine clinical trials

From the broader perspective of CAM more generally, an Australian study found that as many as 40% of OA sufferers used CAM.(Zochling et al., 2004) A systematic

review indicated the incidence of adverse effects associated with herbal medicine treatment of OA appeared to be low, and that herbal medicine (in general) may offer a much-needed alternative for individuals with long-term chronic OA.(Long et al., 2001) Herbal medications are commonly used for rheumatic conditions.(Setty and Sigal, 2005)

Studies of the efficacy of CHM treatment of OA of the knee are set out in Table 5.1. The majority are published in Chinese. Other articles identified in the literature search that are published in English relate to studies of single herbs (or single herb extracts) or Ayurvedic medicine and are not guided by Syndrome differentiation,(Kang et al., 2005) and since single herbs are rarely prescribed in CHM those studies were not included.

An examination of the studies and the medicinal formulae investigated summarised in Table 5.1 suggests that OA of the knee is typically treated as Bi Syndrome, particularly Bi Syndrome of Bone, in which Kidney deficiency was regarded as the root of the OA pathogenesis accompanied by Blood Stasis. Most of the CHM used in these studies were, overall, warm in nature, and based on the treatment principles of tonifying the Kidney and promoting Blood circulation.

In general, the majority of Chinese studies suffered from methodological short-fallings, a finding similar to the conclusion of another survey conducted on quality of RCTs reported in Chinese journals.(Wang et al., 2007a) Only two studies set out in Table 5.1 that were published in Chinese were double-blinded and randomised.(Cao et al., 2004b, Ge et al., 2002) Methodological problems include not using reliable diagnostic criteria, appropriate study design and/or appropriate statistical analysis, issues also noticed by other researchers.(Cao et al., 2006b, Li, 2003a) The Jadad scores for the majority of the studies are low. (see the Table 5.1) Appraisal of the CONSORT checklist for the studies identified (see the Table 5.2) indicated several methodological problems including a lack of information about the herbal products, qualitative testing of the herbs, rationale for the type of control used and information about the practitioners taking part in the studies. In addition, several did not report sample size, method of randomisation and the allocation concealment, as well as the details of the study implementation, and whether there was blinding. None of the

studies described the protocol with respect to flow of procedures or participants through the study.

Comparability across studies is difficult due to the range of diagnostic and treatment assessment criteria used. Many Chinese researchers are not familiar with classification criteria for OA that are commonly accepted and used in western countries, the criteria of the American College of Rheumatology being the most widely known in China. Lack of rigor in clinical trials in general has been recognized as a problem and measures introduced consequently within China. For example, the State Food and Drug Administration (China)'s *Clinical Research Guidelines of New Chinese Medicine* (Zheng, 2002) and the State Administration of Traditional Chinese Medicine's *Criteria of Diagnosis and Therapeutic Effect of Disease and Syndromes in Traditional Chinese Medicine* (The State Administration of Traditional Chinese Medicine, 1994) have been published to guide the conduct of clinical trials.

5.6.2 Results of acupuncture research

Limited scientific evidence from RCTs suggests that acupuncture is useful for pain control and that it can improve physical dysfunction associated with knee OA.(Selfe and Taylor, 2008) However, many studies have methodological shortcomings, including lack of evidence of randomisation and blinding, lack of an adequate placebo control and lack of use of validated assessment tools.(Li et al., 2007a)

The literature search revealed 33 clinical trials that have investigated the efficacy of acupuncture in the treatment of OA of the knee, set out in Table 5.3. Of these, 27 were conducted in China, all suggesting that acupuncture was effective. Several assessed multiple treatment modalities, making it difficult to reach any conclusions about efficacy of acupuncture itself. Some studies utilised different treatment periods within the study. Several used unreferenced treatment assessment criteria and did not use accepted OA diagnostic criteria. There was no information provided regarding the level of clinical experience and training background of the acupuncturists involved in the studies. Very few reported safety data or compliance data. The majority did not give any description of blinding, therefore the reader cannot be sure that this occurred. Jadad scores for many of the studies are again low. Analysis of study methodology using the CONSORT checklist (set out in Table 5.4) also indicates that the quality of reporting in the majority of Chinese studies was poor. In addition, other problems

included lack of precise details about the interventions (i.e. acupuncture or combined treatment) intended for each group, and how and when the interventions were actually administered. There was a lack of information about whether or how the interventions were standardised and compliance of the acupuncturists with the acupuncture protocol. The majority of the articles did not report how sample size was determined, which methods were used to generate the random allocation sequence, and whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment.

There were six studies conducted in western countries, five supporting the contention that acupuncture is significantly more effective in relieving pain and improving knee function in OA sufferers in comparison with either placebo or another active intervention.(Berman et al., 2004, Berman et al., 1999, Sangdee et al., 2002, Vas et al., 2006, Witt et al., 2005) One clinical trial found that the effect of acupuncture for pain relief decreased over a 12 month follow-up period in comparison to a control group who had superficial needling.(Witt et al., 2005) The one RCT (Scharf et al., 2006) that found that acupuncture was no better than placebo but better than conservative therapy could be criticised for imperfect blinding and the sham acupuncture procedure used as a control.(Selfe and Taylor, 2008, Muramatsu, 2007, Wettig, 2007) It is well recognised within the field of acupuncture research that one of the difficulties of research is the identification of an appropriate placebo control, often termed ‘sham’ treatments.(White et al., 2007b)

Systematic reviews and meta-analyses are equivocal with respect to efficacy evidence. One meta-analysis concluded that the clinical improvements of acupuncture may be due to placebo or expectation effects.(Manheimer et al., 2007) Another systematic review found acupuncture superior to sham acupuncture for treating chronic knee pain in both the short and longer term.(White et al., 2006) Systematic reviews of acupuncture studies in OA indicate that there were no adverse events associated (Manheimer et al., 2007, White et al., 2006, Yamashita et al., 2006) and that acupuncture is a relatively cost-effective therapy for OA patients.(White and Kawakita, 2006, Witt et al., 2006)

Commonly used acupoints in clinical trials include the acupuncture points: ST-35 (Stomach meridian point no. 35, Du Bi), ST-36 (Zu San Li), GB-34 (Gallbladder

meridian point no. 34, Yang Ling Quan) and SP-9 (Spleen meridian point no. 9, Yin Ling Quan), and EX-LE-4 (Extra point, Nei Xi Yan).(Li et al., 2007a, Selfe and Taylor, 2008)

Only one study published in English has investigated the efficacy of moxibustion therapy in OA. (Vas et al., 2004) Moxibustion is the external use of a dried Chinese herb Ai Ye, often in the form of a cigar-like stick or placed within a wooden box, that is lit then allowed to smoulder and placed near an acupuncture point to warm the meridians: the heat and the fragrant properties are thought to cause the therapeutic effect. The study reported that 75% of patients gained moderate clinical improvements and patients consumed less analgesics and anti-inflammatory drugs during the trial. However, the moxibustion treatment was combined with electro-acupuncture and auricular therapy during the treatment period; furthermore, there was neither the control group nor randomisation information in the study. Chinese studies of moxibustion found that moxibustion significantly improved symptoms of OA in comparison with controls,(Li et al., 2008, Sun et al., 2008, Fu et al., 2007, Huang, 2002, Li et al., 2002) however these studies had methodological problems so caution needs to be taken in interpreting results.

5.7 Conclusion

OA has been traditionally treated as Bi Syndrome in CM. Many clinical trials of CHM for the treatment for OA have been conducted to verify their efficacy, but the quality of the studies has generally been poor. Although there have been a few more rigorous RCTs investigating the efficacy of acupuncture in OA treatment that suggest acupuncture may be useful in alleviating pain and improving knee function, the results are not conclusive. The majority of studies conducted in China have also been methodologically flawed. Therefore, there is a need for high quality clinical research into the treatment of OA with CM.

The concept of Bi Syndrome covers a range of rheumatologic diseases, not just OA. Fundamentally the aetiology and pathogenesis is understood to be related to Kidney Deficiency accompanying by an invasion of exogenous Wind, Damp and Cold. An emerging theory considers OA as a combination of Wei Syndrome and Bi Syndrome which is readily explainable using CM theory and has some support from animal

studies and anecdotally from clinical practice. There were some studies supporting CHM treatment targeting the Liver organ, but the quality of those trials is of concern.

Guided by this emergent theory, a new formula was created, based on one used in a relatively well-designed study (Cao et al., 2004b) conducted in China. This formula, named the Bai Niu Capsule, emphasises the treatment strategies of nourishing the Liver and Kidney and to a lesser extent expelling Wind, Dampness and Cold, and is the subject of the remainder of this thesis.

Table 5.1 Clinical studies of Chinese herbal medicine treatment for OA of the knee

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Tang et al., 2003)	60 (treatment group n=30, control group n=30) No information of dropouts	63.5	28 : 32	No information	Parallel design. No description of randomisation. & blinding 4 weeks treatment period	Treatment group: Gu Yan Ding Decoction oral administration plus external application 1 package per day (Pu Gu Zhi 12g, Gu Sui Bu 12g, Niu Xi 12g, Hong Hua 5g, Huang Qi 20g, Mu Gua 15g) Control group: Acetaminophen 0.9g Tid. Po. (Oral administration only)	ACR 1986; and TCM syndrome differentiation (Deficiency of Kidney and Liver, accompanying with Blood stagnation)	No information	No information	No information	① Activities of Daily Living Scale of the Knee (ADLS)	Within group analysis: Gu Yan Ding significantly increased the scores of symptoms, activity function and overall scores of ADLS ($p<0.01$); Between groups analysis: Significant improvement in total score on ADLS in Gu Yan Ding group ($P<0.05$).	0
(Zheng and Cheng, 2004).	60 (treatment group only, no control group) 6 dropouts; 3 excluded in screening	55.4	Female only	No information	Open label trial. No description of randomisation. & blinding 1 month treatment period.	Treatment group: Gu Shu Kang granules (Yin Yang Huo, Shu Di Huang, Huang Qi, Dan Shen, Gu Sui Bu made by Healthstar Medical Development Co. Beijing)	ACR 1991; and TCM syndrome differentiation (Deficiency of Kidney)	No information	No information	No information	① Activities of Daily Living Scale of the Knee (ADLS) ② Serum estradiol level test	Within group analysis: Gu Shu Kang significantly reduced pain and improved scores of knee functional assessment ($p<0.01$); serum estradiol level rose after treatment ($p<0.05$).	1

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Ruan et al., 2005)	120 (TCM group n=30; Estradiol group n=30; TCM + estradiol group n=30; Non-treatment group n=30) No drop-out patient	52±5 (three treatment groups) 54±5 (Non-treatment group)	Female only	No information	Parallel study design. RCT, but no description of randomisation. Single blind (assessor blinded) 12 weeks treatment period	Treatment group: Qiang Gu Capsule (flavone of rhizoma drynariae produced by Beijing Qihuang Pharmaceutical Factory) Control group medication: Estradiol 0.5-1.5mg qd. Po. (individualised dosage used in the trial)	ACR 1995	No information	No information.	Yes. No adverse events found	① Effective range of the motion of knee	Improvement found in all three treatment groups ($p<0.01$). TCM + estradiol group significantly improved motion range compared with other groups (TCM group and estradiol group) ($p<0.01$), but estradiol group had similar effect to TCM group.	2
(Shi et al., 1994).	262 (treatment group n=50; TCM control group n=24; Fenbid control group n=188) No information of dropouts	No info	95 :167	No information	Parallel study design (3 groups) No information of randomisation & blinding 4 weeks treatment period	Treatment group: Yang Xue Ruan Jian Decoction (Bai Shao, Mu Li, Qin Jiao, Gan Cao, manufacturer name not given) 70 ml per day TCM control group: Tonifying Kidney and Strengthening Bone Decoction, 70 ml per day Western medicine control group: Fenbid (Ibuprofen): no dosage description given	ACR (no citation of year of publication)	No information	No information	No information	① Author-created OA scale scores (referred to articles of Lequesne MG et al & Goldberg VM et al)	Significant difference between Treatment group and Fenbid Control group for an OA score improvement of ≥10' ($p<0.05$). Highly significant difference between Treatment group and Fenbid group ($p<0.01$) for an OA score improvement of ≥20. Significant difference between Treatment group and TCM Control group in terms of OA scores ($p<0.05$).	0

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Cao et al., 2004b)	120 (the first trial: treatment group n=30, control group n=30; the second trial: treatment group n= 30, control group n=30) No drop-out patient	the first trial: 58±7 (treatment group) and 59±9 (control group) the second trial: 64±9 (treatment group) and 62±9 (control group)	the first trial 21:39 the second trial 19:41	Yes	The first trial: parallel study design, double blind RCT. The second trial: parallel design, no blinding, RCT 4 weeks treatment period (for each trial)	Treatment group medication: Yang Xue Ruan Jian Capsule (Bai Shao, Mu Li, Qin Jiao, Gan Cao) 1.05g tid. Po. Control: TCM Control medication: Kang Gu Zhi Zeng Sheng Capsule (1.75g tid. Po.); Western medicine Control medication: Glucosamine (0.75g tid. Po.)	ACR 1986	Yes, but no detailed description given	Yes, but no detailed description given.	Yes, 4 adverse events in the treatment group in the first trial; no adverse event in the second trial	① WOMAC index ② Visual Analogue Scale	The analgesic function of Yang Xue Ruan Jian Capsule became apparent during 2- 4 week period, and WOMAC scores of the treatment group decreased after 4 weeks therapy ($p<0.05$). The therapeutic effectiveness was similar across all three groups ($p>0.05$), but the herbal dosage used in the treatment group was less than the contrast herbal group used.	4
(Ge et al., 2002)	200 (treatment group n=100 control group n=100) No drop-out patient	55.87 ± 7.64 (treatment group) & 54.13 ± 7.16 (control group)	57:143	No information	Parallel design double-blind RCT, but no description of randomisation. 1 month treatment period.	Treatment group: compound Du Zhong Jian Gu Granules (Du Zhong, Xu Duan, Niu Xi, Dang Gui etc. 12g qd. Po. Control: Zhuang Gu Guan Jie pill 6g bid. Po. Treatment group: real DZJG plus sham control medicine Control group: sham DZJG plus real control medicine.	Clinical Research Guidelines of New Chinese Medicine - Edition 3 (China) and TCM syndrome differentiation (Deficiency of Kidney and Liver, accompanying with Blood stagnation)	No information	No information	Yes. no trial related adverse event found except for some digestive discomfort (no detailed information)	① Joint function scale scores based on Clinical Research Guidelines of New Chinese Medicine - Edition 3 (China)	Compound DZJG was superior to the control group in the total effective rate ($p<0.01$) and TCM signs ($p<0.01$); Two drugs both could improve the symptoms in within group analysis ($p<0.01$); but no significant difference between two groups ($p>0.05$), and DZJG got better response in patients with mild OA rather than moderate and severe OA.	3

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Wang et al., 2004)	400 (treatment group n=300, control group n=100) No drop-out patient	the treatment group: ≤ 50yrs (69 patients), 51-60yrs (131 patients), 61-70yrs (100 patients)	78:222 (treatment group) No information of the control group	No information	RCT, but no information of randomisation & blinding 1 month treatment. period	treatment group: compound Du Zhong Jian Gu Granules (DZJG Granules) (Du Zhong, Xu Duan, Niu Xi, Dang Gui etc. produced by Tianjin Lisheng Pharmaceutical Co.Ltd.) 12g qd. Po. control group medication: Zhuang Gu Guan Jie Pill 6g bid. Po	Clinical Research Guidelines of New Chinese Medicine - Edition 3 (China) & TCM syndrome differentiation (Deficiency of Kidney and Liver, accompanying with Blood stagnation)	No information	No information	Yes, no trial related adverse event found except for 3 patients having digestive discomfort (no detailed information)	① Joint function scale scores based on Clinical Research Guidelines of New Chinese Medicine - Edition 3 (China)	Compound DZJG was superior to the Control group in the total effective rate ($p<0.01$), time to response ($p<0.01$) and in terms of TCM signs ($p<0.01$);. Within groups analysis indicated an improvement in symptoms compared with pre-treatment in both Treatment group and Control group ($p<0.01$).	2
(Zhang et al., 2000)	100 (treatment group only) No information of dropouts	57.2 ± 6.8	38 : 62	No information	Open label study 6 weeks treatment period	treatment group: Zhui Feng Tou Gu Pill (Zhi Chuan Wu, Bai Zhi, Xiang Fu, Bai Zhu, Chuan Xiong, Dang Gui, Ru Xiang, Mo Yao, Qin Jiao, Qiang Huo, Tian Ma, Gan Cao, Guangzhou Jing Xiu Tang Pharmaceutical Company Ltd) 6g tid. Po	ACR (no citation of year of publication) & Clinical Criteria of TCM Syndrome Differentiation (Shanghai Health Bureau, 1998) including 3 patterns	Yes	No information	Yes. No adverse events being reported.	① Clinical efficacy based on Clinical Efficacy Criteria of TCM Syndrome Differentiation (Shanghai)*	ZFTG Pill improved clinical symptoms ($p<0.01$).	0
(Jiang, 2005)	150 (treatment group n=80 control group n=70) No information of dropouts	62.41 ± 6.11 (treatment group) 63.62 ± 5.31 (control group)	28 : 52 (treatment group) 24 : 46 (control group)	No information	Parallel design, an RCT but no detailed information of randomisation. No blinding. 3 months treatment period	treatment group: Individualised CHM Decoction according to TCM syndrome differentiation control group: Sulindac (150mg bid. Po.) + Glucosamine Sulfate (500mg qd. Po.)	Clinical Research Guidelines of New Chinese Medicine (China 2002)	No information	No information	No information	① Clinical efficacy based on Clinical Efficacy Criteria of Clinical Research Guidelines of New Chinese Medicine (China)	TCM decoctions were significantly superior to control group medication in reduction of clinical symptom scores ($p<0.01$).	1

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Zhou et al., 2006a)	60 (treatment group n=29; control group n=26) 1 drop-out in the treatment group and 4 drop-outs in the control group	56.90 ± 7.09 (treatment group) 57.73 ± 7.44 (control group)	10 : 19 (treatment group) 8 : 18 (control group)	No information	Parallel design, RCT, but no detailed information on randomisation & no information of blinding 6 weeks treatment period	treatment group: Guan Jie Kang Tablet (Shu Di Huang, Niu Xi, Du Zhong, Gou Qi Zi, Dan Shen, Hong Hua, Mu Xiang, Bu Gu Zhi etc.) 23.68g tid. Po control group medication: Celecoxib 200mg qd. Po.	ACR1995; TCM Syndrome differentiation (based on ranking symptoms, no pattern being assessed)	Yes, no detailed information	No information	No information	① Author-created TCM Symptom Scale developed from WOMAC index and Lequene knee osteoarthritis index	Clinical improvement after treatment within both Treatment and Control groups ($p<0.01$). GJK Tablet had the same therapeutic effectiveness as Celecoxib ($p>0.05$) with respect to the TCM symptom scale. GJK Tablet was more effective than Celecoxib in altering TCM signs and symptoms ($p<0.01$)	2
(Hu et al., 2001)	60 (treatment group n=30 control group n=30) No information of drop-outs	No information	9 : 21 (treatment group) 8 : 22 (control group)	No information.	Parallel design. RCT, using random number table. No information of blinding. 4 weeks treatment period	treatment group: Zheng Qing Feng Tong Ning Tablet (Sinomenine) 60mg tid. Po. control group: Zheng Qing Feng Tong Ning (ZQFTN) tablet (Sinomenine) 60mg tid. Po. plus Chloropheniramine (4mg tid. Po) in first two weeks.	Author created without citation (based on X Ray evidence, age over 40, knee inflammatory symptoms, crepitus, oedema etc.)	No information	Yes, but no detailed information	Yes, 16 adverse events reported: 6 in the control group, 10 in the treatment group, including dry mouth, drowsiness, itching, and stomach discomfort.	① Clinical efficacy created by authors ② Ranking system based on symptoms and signs and the degree of them (Likert scale).	Within group analysis indicated there were significant improvements in symptoms according to rating scores in both groups ($p<0.001$). The two groups had similar clinical responses ($p>0.05$). There was no significant difference in the rate of side effects between two groups. ($p>0.05$).	1
(Wu et al., 2001)	100 (treatment group n=21; control group n=21; another open label trial n=58) No information	40.71±12.77 (treatment group) 36.86±14.37 (control group) 49.39±10.83 (open	16 : 5 (treatment group) 17 : 4 (control group) 23 : 35 (open	No information	Parallel design. RCT, but no detailed information of randomisation. No information of blinding.	treatment group: Yao Tui Tong pill 1.2g bid. Po. control group: Yao Tong Ning capsule (TCM patent medicine) 1.5g qn. Po.	No information of diagnosis criteria, but included all kinds of joint diseases even lumbar muscle strain and sciatica.	Yes, but excluded patient from the trial who was taking any other medication	No information	Yes, 3 adverse events reported in the open label trial	① Clinical efficacy created by authors without citation	no statistical analysis conducted in within group analysis Ridit analysis indicated the treatment group was more effective than the control group in symptoms and signs relief ($p<0.05$)	1

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
	of dropouts	label trial)	label trial)		37 days treatment period	open label trial: Yao Tui Tong pill 1.2g bid. Po.	TCM diagnosis as Bi syndrome of Cold and Damp blockage pattern					Effectiveness was 96.55% in the open label trial.	
(Liu and Zhou, 2004)	120 (treatment group n=64; control group n=56) No information of dropouts	No information	51 : 69	No information	Parallel design. RCT, using random number table but no detailed information No information of blinding. 2 weeks treatment period, follow-up over 1 year	treatment group: modified Tong Yong Tong Feng (TYTF decoction) (individualised raw herbs decoction) control group: Indomethacin (50mg tid. Po.), reduced to half dosage when pain eased.	refer to Clinical Research Guidelines of New Chinese Medicine (China 1989)	No information	No information	No information	①Clinical efficacy (referred to Clinical Research Guidelines of New Chinese Medicine, China)	TYTF decoction more effective than indomethacin in improving knee motion ($p<0.05$), but no significant difference in knee pain ($p>0.05$) Overall effectiveness of TYTF decoction group was significantly better than in the control group ($p<0.05$).	2
(Dang et al., 2003)	118 (treatment group n=60; control group n=58) No information of dropouts	60 (treatment group) and 61 (control group)	32 : 28 (treatment group) 30 :28 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation No information of blinding. 15 days treatment period.	treatment group: Qiang Jin Jian Gu (QJJG) pill (Shaanxi Chenji Pharmaceutical Co. Ltd.) 1.8g bid. Po. control group medication: Ibuprofen 0.3g tid. Po.	No information of diagnostic criteria.	No information	No information	No information	① Clinical efficacy created by authors without citation	Effectiveness of QJJG pill (90%) was greater than efficacy of Ibuprofen (70.67%) however there was no statistical analysis performed.	1

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Yang et al., 2003)	50 (treatment group n=300; control group n=150) No information of dropouts	44	149:151 (treatment group) 76:74 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation procedure. No information of blinding. 1-3 months treatment period (not a fixed period)	treatment group: Mu Gua Wan (herbal medicine in pill form, Hubei Guangren Pharmaceutical Co. Ltd.) 6g tid.Po. control group medication: Oxaprozine 0.2g bid. Po.	According to Diagnostic Criteria of National Rheumatology Conference (China) 1988 - including OA, ankolysing spondylitis, and atrophic arthritis TCM syndrome differentiation (Deficiency of Qi and Blood with Cold and Damp blockage in Channels)	Yes, stopped all other medication	No information	Yes. No adverse events in treatment group, however some cases (no data) of leukopenia and gastrointestinal discomfort in the control group.	① Clinical efficacy created by authors without citation	Mu Gua Pill improved symptoms and had a similar effect to Oxaprozine (p>0.05). Authors concluded that Mu Gua Pill was suitable for the treatment of all three diseases.	1
(Guo, 2006)	90 (treatment group n=60; control group n=30) No information of dropouts	51 (treatment group) 53 (control group)	15:45 (treatment group) 9:21 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation procedure. No information of blinding. 5 weeks treatment period.	treatment group: Jin Gu Tong Xiao (JGTX) pill (Henan Luozheng Pharmaceutial Company) 6g bid. Po. plus sodium hyaluronate injection 2ml qw. in vitro. control group medication: sodium hyaluronate injection 2ml qw. in vitro.	Diagnostic Criteria of Osteoarthritis 2003 (recommended by Chinese Medical Association, PR China) TCM syndrome differentiation referred to the pattern of Blood stasis accompanying with Cold invasion	No information	No information	No information	① Clinical efficacy and function scale created by author (no reference given)	Patients treated with JGTX Pill plus sodium hyaluronate injection achieved a greater clinical effective rate (p<0/05) and there was also a significant improvement in symptoms and physical signs within the Treatment group (p<0.05)	1

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Du and Zhu, 2005)	60 (treatment group only) No information of dropouts	No information	23 : 37	No information	Open label trial.(no control group) No information of blinding 4 weeks treatment period	treatment group: Jin Wu Gu Tong Capsule (herbal patent medicine, Guizhou Shenqi Shengshi Pharmaceutical Co. Ltd.) 1.05g tid. Po.	Diagnostic Criteria of Osteoarthritis 2003 (Chinese Medical Association, China) TCM syndrome differentiation - pattern of Deficiency of Kidney and Liver accompanying with Cold and Damp invasion	Yes, stopped all other medication	No information	No information	① Knee function scale created by the author (no reference given).	JWGT capsule improved symptoms in knee pain, lassitude in legs, stiffness, numbness, functional disability and local tenderness ($p<0.01$), and coldness of knee ($p<0.05$).	0
(Xie, 2005)	88 (treatment group n=44; control group n=44) No information of dropouts	56.81±5.81 (treatment group) 57.12±6.01 (control group)	12:32 (treatment group) 11:33 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation No information of blinding. 4 weeks treatment. period	treatment group: Modified Si Xian Xu Duan Decoction (Du Zhong 12g, Xu Duan 12g, Wu Jia Pi 10g, Fang Feng 6g, Yi Yi Ren 15g, Qiang Huo 10g, Dang Gui 9g, Niu Xi 10g, Tu Bie Chong 9g,) control group medication: Zhuang Gu Guan Jie Pill (a herbal patent medicine) 6g bid. Po.	ACR (no citation of year of publication) No information of TCM diagnosis	No information	No information	No information	① Clinical efficacy (referred to Clinical Research Guidelines of New Chinese Medicine, China - no information of edition)	Clinical effective rate was higher and greater improvement in symptoms in modified SXXD Decoction group in comparison to Control group ($p<0.05$)	1

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Li and Zhou, 2005)	70 (treatment group n=50 control group n=20) No information of dropouts	56.8 (treatment group) 55 (control group)	13:37 (treatment group) 4:16 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation. No information of blinding. 6 weeks treatment period but some received only 3 weeks treatment according to its protocol	treatment group: Gui Yuan San (herbal formula) oral decoction + external application once a day control group medication: Ibuprofen 0.3g tid. Po.	ACR 1986 and TCM syndrome differentiation of Deficiency of Kidney and Liver accompanying with Blood stagnation	No information	No information	Yes, only 14 adverse events of digestive system in the control group	① Clinical efficacy (no description of criteria)	Improvement in symptoms in GYS Decoction group significantly greater than in Control group ($p<0.01$).	1
(He et al., 2005)	96 (treatment group n=47 control group n=49) No information of dropouts	56.1±12.9 (treatment group) 57.2±13.7 (control group)	22:25 (treatment group) 25:24 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation. No information of blinding 4 weeks treatment period	treatment group intervention: arthroscopic operation + individualised CHM decoction in post-operation period (based on the principle of Qi-invigorating, kidney-supplementing, blood-activating) control group intervention: arthroscopic operation only	ACR 1995 No information of TCM diagnosis	No information	No information	No information	① Clinical efficacy rating scale (referenced to a Chinese publication) ② the level of IL-1, IL-6 in serum and synovial fluid	treatment group was superior to the control group in clinical effective rate ($p<0.05$); the level of IL-1 and IL-6 in serum and synovial fluid significantly declined after treatment in both groups; and the change in IL-1 and IL-6 was greater in the TCM group in comparison to the control group ($p<0.05$). The recurrence rate of knee OA in the TCM group was 7.9% and 30.3% in the control group.	1

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Le and Du, 2004)	60 (treatment group n=30 control group n=30) No information of dropouts	62 (treatment group) 61 (control group)	8:22 (treatment group) 10:20 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation No information of blinding. No information of treatment period.	treatment group: No.1 Gu Guan Jie Yan decoction (Yin Yang Huo 30g, Ba Ji Tian 30g, Chuan Xiong 9g, San Qi 3g, Zu Shi Ma 12g) control group medication: Diclofenac 75mg qd. Po.	ACR1995 No information of TCM diagnosis	No information	No information	No information	① Knee function scale (referenced to the Clinical Research Guidelines of New Chinese Medicine 2002)	Two groups had significant effective rate compared with pre-treatment ($p<0.01$). TCM decoction had a similar effect as Diclofenac in symptoms improvement ($p>0.05$) but was better in relieving morning stiffness ($p<0.05$).	1
(Qi et al., 2005)	120 (treatment group n=64 control group n=56) No information of dropouts	64.2	68:52	No information	Parallel design. RCT, but no detailed information of randomisation. No information of blinding. 2 weeks treatment period with follow-up period of 1 year.	treatment group: Fu Yuan Rong Gu Tang (herbal formula) oral decoction + external application control group medication: Diclofenac 75mg Bid. Po.	ACR 1986 No information of TCM diagnosis	No information	No information	No information	① Clinical efficacy (recommended by National Criteria of Diagnosis and Treatment in TCM 1994)	TCM Decoction and Diclofenac had similar clinical efficacy ($p>0.05$), but was better in reducing the recurrence rate of knee OA ($p<0.05$).	1
(Liu, 1995)	76 (treatment group only) No information of dropouts	57	25:51	No information	Open label trial, no control group. Treatment periods varied between 1 and 6 phases (1 phase of treatment=15 day)	treatment group: individualised raw herbal medicine decoction based on principle of nourishing the Liver plus self-massage therapy.	The Surgery Textbook of China High Education of Medical University (1980)	No information	No information	No information	① Clinical efficacy (no reference given)	Efficacy was 93.4%, and minimum treatment period was 1 phase, maximum was 6 courses. The author thought the study demonstrated nourishing Liver and relaxing Sinews was an effective principle for OA	0

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Chen, 1995)	85 (treatment group only) No information of dropouts	42.1	28:57	No information	Open label trial (no control group) the treatment period varied between 2-8 weeks) Follow-up period was also unfixed from 2 months to 2 years	treatment group: individualised modified Dang Gui Si Ni Tang (herbal decoction)	No information	No information	No information	No information	① Clinical efficacy (referenced to O'Connor's Textbook of Arthroscopic Surgery 1st edition, 1984)	Effective rate was 95.27%, marked effective rate was 68.23%; and minimum treatment period was 2 weeks, maximum was 8 weeks. Authors claim the study demonstrated that 'Warming and Nourishing Liver Blood' was a feasible treatment principle for OA.	0
(Fan, 2006)	65 (treatment group n=35 control group n=30) No information of dropouts	52.66±7.05 (treatment group) 50.07±6.98 (control group)	20:15 (treatment group) 18:12 (control group)	No information	Parallel design. RCT, but no information of randomisation. No information of blinding 1 month treatment period.	treatment group: Bu Shen Zhuang Gu Decoction (herbal formula) control group: Zhuang Gu Guan Jie Pill (herbal patent medicine) 6g bid. Po.	Diagnosis criteria referred to Clinical Handbook of orthopaedics 1st ed (ISBN :7-117-01685-X)	No information	No information	Yes, but no information of adverse event	① Clinical efficacy ② symptom ranking score (no reference)	Efficacy of the treatment group was 94.29% significantly greater than that of control group (86.67%) ($p<0.05$). Within group analysis: symptom ranking scores in both groups were significantly lower after treatment compared with baseline ($p<0.05$).	1
(Liu and Fu, 2004)	106 (treatment group n=53 control group n=53) No information of dropouts	56.81±5.81 (treatment group) 57.12±6.01 (control group)	16:37 (treatment group) 14:39 (control group)	No information	Parallel design. No information of randomisation No information of blinding No information of treatment period.	treatment group: Bu Xi Decoction (herbal formula) control group: Zhuang Gu Guan Jie Pill (herbal patent medicine) 6g bid. Po.	ACR (no information of year of publication)	No information	No information	No information	① Clinical efficacy (referred to Clinical Research Guidelines of New Chinese Medicine, China)	The efficacy of the treatment group (39.99%) was significantly greater than the control group (22.64%) ($p<0.05$) but there was no difference between the groups in terms of overall effectiveness rate.	0

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Chen et al., 2005)	94 (treatment group n=49 control group n=45) No information of dropouts	56.8 (treatment group) 57.4 (control group)	17:28 (treatment group) 19:26 (control group)	No information	Parallel design. No information of randomisation and blinding 30 days treatment period	treatment group: author-created formula (herbal decoction based on the principle of Tonifying Kidney and Invigorating Blood) control group medication: Fenbid (Ibuprofen) 300mg bid. Po.	Criteria of Diagnosis and Therapeutic Effect of Disease and Syndromes in Traditional Chinese Medicine (China)	1 week washout period but no information of concomitant medicine	No information	No information	① Clinical efficacy (referred to Criteria of Diagnosis and Therapeutic Effect of Disease and Syndromes in Traditional Chinese Medicine, China)	Efficacy of the treatment group (93.9%) was significantly greater than Control group (84.4%) ($p<0.05$)	0
(Bian and Zhou, 2005)	60 (treatment group only) No information of dropouts	61.3	32:28	No information	Open label trial. No information of randomisation and blinding, no control group No information of treatment period.	treatment group: Bu Shen Zhuang Jin Decoction (herbal formula)	There was X-ray diagnosis criteria of osteoporosis only	No information	No information	No information	① Pain scale (referred to criteria in another Chinese publication 2003) ② Bone densitometry	Significant difference in pain scores before and after treatment ($p<0.05$), but no significant change in bone mineral density ($p>0.05$).	0
(Li et al., 2003)	661 (treatment group n=495 control group 166) No information of dropouts	56.75±3.25	319:276	No information	Parallel design. RCT; the random number table applied No information of blinding 3 months treatment period and 3 months follow-up	treatment group: Gu Bi capsule (herbal patent medicine) 0.6g tid. Po. control group: Zhuang Gu Guan Jie pill (herbal patent medicine) 6g bid. Po.	① Criteria of Diagnosis and Therapeutic Effect of Disease and Syndromes in TCM; ② Level of bone mineral density	Yes, exclude any other medication in the trial	No information	Yes, 35 adverse events in the treatment group including dizziness, gastrointestinal discomfort; no information of the control group	① Clinical efficacy ② Bone mineral density ③ X-ray signs	Efficacy of the treatment group (95.76%) was significantly greater than that of Control group (89.16%) ($p<0.01$), even after 3 months follow-up period. Change of bone mineral density in intra-groups analysis was significant different $p<0.05$) after treatment.	2

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
												Some improvements in X Ray signs in the treatment group but no statistical analysis was performed.	
(Zhu and Ning, 2002)	63 (treatment group n=36 control group n=27) No information of dropouts	58.9 (treatment group) 55 (control group)	8:28 (treatment group) 6:21 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation each group had been stratified into two sub-groups according to Indices of Severity for Osteoarthritis. 2 month treatment period, and 1 month follow-up	treatment group: Huang Qi Gui Zhi Wu Wu Capsule (herbal patent medicine) 1.35-1.8g tid. Po. control group medication: Fenbid (Ibuprofen) 300mg bid. Po.	ACR 1986; no information of TCM diagnosis	No information	No information	No information	① Indices of Severity for Osteoarthritis (ISOA) (referred to Lequesne M. Indices of severity and disease activity for osteoarthritis. Seminars in Arthritis and Rheumatism. 1991;20(6, Suppl 2):48-54)	There was significant change in ISOA after treatment by comparison with baseline ($p<0.01$) for the treatment group of mild and moderate stage OA, but no statistical difference for advanced stage OA patients ($p>0.05$) No statistically significant difference in ISOA in control group before and after treatment in any stage of OA ($p>0.05$).	1
(Zheng et al., 2006a)	32 (treatment group only) No information of dropouts	63.5	12:20	No information	Open label trial no control group. No information of blinding 30 days treatment period	treatment group: Jin Gu Tong Xiao Pill (herbal patent medicine, Henan Luozheng Pharmaceutical Company)	ACR 1995 & TCM syndrome differentiation of the pattern of Blood stasis and Cold retention	No information	No information	No information	① Author created TCM Activity Daily Life (ADL) scale (referred to three publications) ② SF-36 Questionnaire	Jin Gu Tong Xiao pill significantly improved TCM ADL scores ($p<0.01$). All measurement dimensions of SF-36 Questionnaires has been improved ($p<0.01$).	0

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
(Xiao et al., 2005)	118 knees (treatment group n=58 control TCM group n=35 control Western medicine group n=25) No information of dropouts	No information	No information	No information	Parallel design. RCT, but no detailed information of randomisation and blinding 15 days treatment period for the treatment group and control TCM group 10 days treatment. period for the control Western medicine group	treatment group: external application of Feng Shi Gu Tong medicinal liniment once in two days + a hammer-like head filled in the same medicine tapped against the knees control TCM group: the same medicine applied topically plus local massage twice daily. control Western medicine group: Dinclofenac Sodium 25mg bid. Po.(10 days)	Author-created and no detailed information of diagnostic criteria	No information	No information	No information	① Author created knee function scale. (no reference)	There were significant changes in knee function score within groups for treatment group and control Western medication group ($p<0.01$), but no significant difference between Treatment group and Control western medicine group after treatment ($p>0.05$).	1
(Zhou, 2003)	220 (treatment group n=160 control group n=60) No information of dropouts	56.28±3.48 (treatment group) 53.46±3.61 (control group)	78:82 (treatment group) 40:60 (control group)	No information	Parallel design. RCT, but no detailed information of randomisation and no information of blinding 2 months treatment period.	treatment group: compound Ruan Shang Shen Jin Pill (herbal patent medicine) 3g tid. Po. control group: Zhuang Gu Guan Jie Pill 6g bid. Po.	Clinical Research Guidelines of New Chinese Medicine (China) 1997	No information	No information	Yes; but no adverse events reported	① Clinical efficacy (no definition given and no reference cited) ② X-ray sign scale	The efficacy of the Treatment group was 99.36% and the control group was 91.66%.	1

Ref.	Sample size and No. of dropouts	Mean age of sample (yr)	Sex ratio (M : F)	Power calculation	Study design	Study intervention / control treatment	Diagnostic criteria	Concomitant medication recorded	Compliance assessed	Safety Monitoring	Outcome Measures	Results	Jadad Scores
.(Zheng et al., 2006b)	72 (treatment group n=36 control group n=36) No information of dropouts	51.06±6.62 (treatment group) 52.78±7.17 (control group)	12:24 (treatment group) 9:27 (control group)	No information	Parallel design RCT, randomisation according to random number table. No information of blinding 3 weeks treatment period and 3 weeks follow-up	treatment group: topical application of Qizheng Qingpeng ointment (herbal medicine) twice per day control group: topical application Votalin Emulgel (Diclofenac Diethylamine Emulgel) twice per day	ACR 1995 and Clinical Research Guidelines of New Chinese Medicine (China) No information of TCM syndrome	No information	No information	Yes; but no adverse events reported.	① Clinical efficacy ② Indices of Severity and Disease Activity for Osteoarthritis (refer to *Seminars in Arthritis and Rheumatism.* 1991;20(6, Supplement 2):48-54.)	① the general efficacy of the Treatment group was 97.22%, whilst the Control group was 88.89% (p>0.05). ② the score of the function scale of the Treatment group was 94.44%, whilst the Control group was 88.89% (p>0.05);	2
(Zhong et al., 2006)	157 (treatment group n=96 control group n=61) No information of dropouts	58.30±7.02 (treatment group) 59.98±7.63 (control group)	24:72 (treatment group) 15:46 (control group)	No information	Parallel design Non-randomisation, no information of blinding 4 weeks treatment; 2 years follow-up.	treatment group intervention: Shu Jin Decoction (herbal formula) fumigation and washing 30min/time, twice per day + isotonic movement of quadriceps femoris muscle 10s/time, 35-50 times= 1 set, 2-4 sets per day control group intervention Shu Jin Decoction fumigation only 30min/time, twice per day	Referred to a Chinese publication, not an official standard	No information	No information	Yes; but no adverse events reported.	① Clinical efficacy and function score (refer to a Chinese publication)	Within group analysis: significant difference in function scores in both groups (p<0.01);. Clinical efficacy significantly greater in the treatment group compared with the control group after treatment and at 2 years follow-up (p<0.05).	0

Key: ACR - American College of Rheumatology; TCM - Traditional Chinese Medicine; CHM - Chinese herbal medicine; Clinical Efficacy Criteria of TCM Syndrome Differentiation (Shanghai) is an official standard that includes disease definition, diagnosis criteria, treatment standards and assessment criteria; Po - ‘per os’(by mouth)

Table 5.2 Published studies of Chinese herbal treatment for OA met the modified CONSORT criteria of herbal interventions

Item	Ref. (Tang et al., 2003)	Ref. (Zheng and Cheng, 2004)	Ref. (Ruan et al., 2005)	Ref. (Shi et al., 1994)	Ref. (Cao et al., 2004b)	Ref. (Ge et al., 2002)	Ref. (Wang et al., 2004)	Ref. (Zhang et al., 2000)	Ref. (Jiang, 2005)	Ref. (Zhou et al., 2006a)	Ref. (Hu et al., 2001)	Ref. (Wu et al., 2001)	Ref. (Liu and Zhou, 2004)
1	×	×	√	×	√	√	√	×	√	√	√	√	√
2	√	√	√	√	√	√	√	√	×	√	√	√	√
3	√	√	√	√	√	√	√	√	×	√	√	√	√
4	√	√	√	√	√	√	√	√	√	√	√	√	√
4A	√	√	√	√	√	√	√	√	√	√	√	√	√
4B	×	×	×	×	√	×	×	×	×	×	×	×	×
4C	√	√	√	×	√	√	√	√	√	√	√	×	√
4D	×	×	×	×	×	×	×	×	×	×	×	×	×
4E	×	×	×	×	√	×	×	×	×	×	×	×	×
4F	×	×	×	×	×	×	×	×	×	×	×	×	×
5	×	√	√	×	√	√	√	×	√	√	√	√	×
6	√	√	√	√	√	√	√	√	√	√	√	√	√
7	×	×	×	×	√	×	×	×	×	×	×	×	×
8	×	×	×	×	√	×	×	×	×	×	√	×	×
9	×	×	×	×	√	×	×	×	×	×	×	×	×
10	×	×	×	×	√	×	×	×	×	×	×	×	×
11	×	×	√	×	√	√	×	×	×	×	×	×	×
12	√	√	√	×	√	√	√	×	√	×	×	√	×
13	×	×	×	×	×	×	×	×	×	×	×	×	×
14	√	√	√	×	×	√	√	×	√	√	×	×	×
15	√	√	√	√	√	√	×	√	√	√	√	√	√
16	×	×	×	×	×	×	×	×	×	×	×	×	×
17	√	√	√	√	√	√	√	√	√	√	√	√	√
18	×	×	×	×	√	×	×	×	×	×	×	×	×
19	×	√	√	×	√	√	√	√	×	×	√	√	×
20	√	√	√	√	√	√	√	√	√	√	√	×	√
21	×	×	×	×	×	×	×	×	×	×	×	×	×
22	×	×	×	×	√	√	×	×	×	√	×	×	×

Table 5.2 Continued

Item	Ref. (Dang et al., 2003)	Ref. (Yang et al., 2003)	Ref. (Guo, 2006)	Ref. (Du and Zhu, 2005)	Ref. (Xie, 2005)	Ref. (Li and Zhou, 2005)	Ref. (He et al., 2005)	Ref. (Le and Du, 2004)	Ref. (Qi et al., 2005)	Ref. (Liu, 1995)	Ref. (Chen, 1995)	Ref. (Fan, 2006)	Ref. (Liu and Fu, 2004)
1	×	×	×	×	√	×	√	×	√	×	×	×	×
2	√	√	√	√	√	√	√	√	√	√	×	×	√
3	×	√	√	√	√	√	√	×	√	√	×	√	√
4	√	√	√	√	√	√	√	√	√	√	√	√	√
4A	√	√	√	√	√	√	√	√	√	√	√	√	√
4B	×	×	×	×	×	×	×	√	×	×	×	×	×
4C	√	√	√	√	√	√	√	√	√	√	√	√	×
4D	×	×	×	×	×	×	×	×	×	×	×	×	×
4E	×	×	×	×	×	×	×	×	×	×	×	×	×
4F	×	×	×	×	×	×	×	×	×	×	×	×	×
5	×	×	√	×	√	√	√	√	√	×	×	×	√
6	√	√	√	√	√	×	√	√	√	√	√	√	√
7	×	×	×	×	×	×	×	×	×	×	×	×	×
8	×	×	×	×	×	×	×	×	×	×	×	×	×
9	×	×	×	×	×	×	×	×	×	×	×	×	×
10	×	×	×	×	×	×	×	×	×	×	×	×	×
11	×	×	×	×	×	×	×	×	×	×	×	×	×
12	×	×	×	√	√	×	√	×	×	×	×	×	√
13	×	×	×	×	×	×	×	×	×	×	×	×	×
14	√	√	√	√	√	√	√	√	√	×	√	×	×
15	√	√	√	√	√	√	√	√	√	√	√	√	√
16	×	×	×	×	×	×	×	×	×	×	×	×	×
17	√	√	√	√	√	×	√	√	√	√	√	√	√
18	×	×	×	×	×	×	×	×	×	×	×	×	×
19	×	√	×	×	×	×	×	×	×	×	×	×	×
20	√	√	√	√	√	√	√	√	√	√	√	√	√
21	×	×	×	×	×	×	×	×	×	×	×	×	×
22	×	×	×	×	×	×	×	×	×	×	×	×	×

Table 5.2 Continued

Item	Ref. (Chen et al., 2005)	Ref. (Bian and Zhou, 2005)	Ref. (Li et al., 2003)	Ref. (Zhu and Ning, 2002)	Ref. (Zheng et al., 2006a)	Ref. (Xiao et al., 2005)	Ref. (Zhou, 2003)	Ref. (Zheng et al., 2006b)	Ref. (Zhong et al., 2006)
1	√	×	√	×	×	×	√	√	×
2	√	√	√	√	√	√	√	√	√
3	√	×	√	√	√	×	√	√	√
4	√	√	√	√	√	√	√	√	√
4A	√	√	√	√	√	√	√	√	√
4B	√	×	×	×	×	√	√	×	√
4C	√	√	×	√	√	√	√	×	√
4D	×	×	×	×	×	×	×	×	×
4E	×	×	×	×	×	×	×	×	×
4F	×	×	×	×	×	×	×	×	×
5	√	×	√	×	√	×	√	√	√
6	√	√	√	√	√	√	√	√	√
7	×	×	×	×	×	×	×	×	×
8	×	×	√	√	×	√	×	√	×
9	×	×	×	×	×	×	×	×	×
10	×	×	×	×	×	×	×	×	×
11	√	×	×	×	×	×	×	×	×
12	√	√	√	×	×	√	×	√	√
13	×	×	×	×	×	×	×	×	×
14	√	×	√	×	√	×	√	√	√
15	√	√	√	√	√	×	√	√	√
16	×	×	×	×	×	×	×	×	×
17	√	√	√	√	√	√	√	√	√
18	×	×	×	×	√	×	×	×	×
19	×	×	√	×	×	×	√	√	√
20	√	√	√	√	√	√	√	√	√
21	×	×	×	√	√	×	×	×	×
22	×	×	×	×	√	×	×	√	√

Table 5.3 Studies of acupuncture treatment for OA of the knee

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Berman et al., 1999)	Total participants n=73. Treatment group n=37 (7 drop-outs) Control group n=36 (8 drop-outs)	Partial crossover design Randomised Assessors blinded 8 weeks treatment period, 4 weeks follow-up	Yes	Treatment group: Needling on GB34, SP9, ST36, ST35, EX-LE4, BL60, GB39, SP6, KI3; Electro-acupuncture between ST35 and EX-LE4. 2 sessions weekly for 8 weeks Control group: Standard care (conventional oral drugs)	ACR criteria 1996	Yes. No side-effects reported by participants.	① WOMAC index ② Lequesne scale	① ② significant difference between groups for all outcomes scores in favour of the Treatment group ($p < 0.001$)	3
(Sangdee et al., 2002)	Total no. participants n=193 Acupuncture treatment group n= 48 (2 dro-outs) Combined treatment group n=49 (3 drop-outs) Comparison Diclofenac group n=49 Control (Placebo) group n=47 (2 drop-outs)	Parallel design Single-blind (patient blinded) Randomised Placebo-controlled (sham) 4 weeks treatment period, 2 months follow-up	No information	Treatment groups: Electro-acupuncture (EA) on ST35, EX-LE4, LI8 and trigger point. Electro between ST-35 and EX-LE4; another pair between LI8 and trigger point. 3 sessions weekly for 4 weeks Combined treatment group: Diclofenac tablet plus EA. Comparison Diclofenac group: Diclofenac tablet plus placebo EA Control (Placebo) group: placebo tablet plus placebo EA (performed by attaching patch electrodes to the same acupoints)	ACR criteria 1995	Yes. 7 patients reported adverse effects (across the three groups)	① Amount of Paracetamol tablets taken per week ② 50 feet walk time ③ Pain VAS ④ WOMAC ⑤ Lequesne functional index ⑥ Physician and patient final opinion of change	① No statistical significance in amount of paracetamol taken between the four groups; ② No statistical significance in 50 feet walk time between the four groups; ③ Mean changes in pain VAS significantly greater in EA group compared with both the Placebo group and the Diclofenac group ($p < 0.05$); ④Combined Treatment group was superior than Placebo group on change of WOMAC pain index ($p < 0.05$) ⑤ Significantly greater change in Lesquesne's functional index in EA in comparison with Placebo group ($p < 0.05$); ⑥ Physician global assessment of EA group were the greatest at week 4 ($p < 0.05$); no statistically significant difference in the number of patient's with overall opinion of 'much better' between the 4 groups.	3

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Berman et al., 2004)	Total no. participants n=570 Real Acupuncture group n=190 (44 drop-outs) Control Sham Acupuncture group n=191 (50 drop-outs) Control: Education group n=189 (81 drop-outs)	Parallel design Randomised Placebo controlled (sham) Patient and assessors blinded 26 weeks treatment period, no follow-up	Yes	Treatment group (Real Acupuncture): Needling on GB34, SP9, ST36, ST35, EX-lE4, BL60, GB39, SP6, KI3, Electro acupuncture on EX-LE4 only; plus 2 sham acupuncture points on abdomen (tapped plastic guide tube on surface of skin). 2 sessions weekly for the first 8 weeks, 1 session weekly for the following 2 weeks, and 1 session biweekly for the next 4 weeks, then 1 session per month for the remaining 12 weeks. Control Sham acupuncture group: real needling on 2 sham points on abdomen and sham acupuncture on the same real points. Control Education group: 6 sessions of education with follow-up post educational materials.	Author defined these but no reference to particular standard (criteria as following: age 50 years or older, diagnosis of OA of knee, radiographic evidence of at least 1 osteophyte at tibiofemoral joint (Kellgren-Lawrence grade ≥ 2), moderate or greater clinically significant knee pain on most days during the past month and willingness to be randomly assigned)	Yes. 26 adverse events were reported, none were due to acupuncture treatment; no significant difference between groups	① WOMAC pain index ② WOMAC function index ③ SF-36 ④ Patient global assessment ⑤ 6 minutes walk	① At end of 26 weeks, significantly greater decrease in WOMAC pain index in true acupuncture group compared with sham acupuncture ($p<0.01$). Significantly smaller change in WOMAC pain index in the Education group compared with the Sham acupuncture group ($p < 0.01$) ② At 26 weeks, significantly greater decrease in the WOMAC function score in the True acupuncture group compared with the sham acupuncture group ($p < 0.01$); significantly smaller decrease in the WOMAC function scale in the Education group compared with the Sham acupuncture group ($p<0.01$) ③ No statistically significant difference between the true and sham acupuncture groups for SF-36 Physical Health score ④ No statistically significant difference between the True acupuncture and Control Sham acupuncture groups in Patient global assessment ⑤ No statistically significant difference between the true and sham acupuncture groups for the 6 minute walk	5

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Witt et al., 2005)	Total no. participants n=294 Acupuncture group n=149 (3 drop-outs) Minimal Acupuncture group n= 75 (4 drop-outs) Waiting list group n=70	Parallel design Randomised Single blind Placebo controlled 8 weeks treatment periods, follow-up at week 26 and week 52	Yes	Treatment group: Needling on 6 local points from ST34, 35, 36, SP9, 10, BL40, KI10, GB33, 34, LI8, and 2 distant points from SP4, 5, 6, ST6, BL20, 57, 58, 60, 62, KI3. 2 sessions weekly in the first 4 weeks and 1 session weekly in the following 4 weeks. Control Minimal Acupuncture group: superficial acupuncture on distant non-acupuncture points; Control Waiting list group: true acupuncture treatment from week 9.	ACR criteria (didn't mention the particular year)	Yes. 9 adverse events (3 in the Treatment group, 2 in the Control minimal acupuncture group, 4 in Control waiting list group); Total 40 side effects reported (24 in the treatment group, 16 in the minimal acupuncture group)	① WOMAC Index	① In the Treatment group, the WOMAC index was significantly lower after treatment in comparison to the minimal acupuncture group and the waiting list group after 8 weeks treatment. ($p < 0.01$), but there was no significant difference after 26 and 52 weeks between the Treatment group and the minimal acupuncture group .	3
(Vas et al., 2006)	Total no. participants n=97 participants (9 drop-outs) Acupuncture group n=48 Control group n=49	Parallel design Randomised, controlled Single blind (patients blinded) 12 weeks treatment period, one month follow-up	Yes	Treatment group (acupuncture): Needling on ST36, GB34, SP9, ST35, EX-LE4; Electro applied, and plus Diclofenac tablet (1 tablet every 8 hours) 1 session weekly for 12 weeks Control group: Streitberger ring (a kind of sham acupuncture with no piercing of the skin, uses an adhesive plaster) applied plus Diclofenac tablet (1 tablet every 8 hours)	Author defined but no reference	Yes, but no data offered.	① WOMAC Index (Likert version) ② Pain VAS	With respect to ① & ② the Treatment group showed significantly greater decreases in index scores than the Control group ($p < 0.01$)	3
(Scharf et al., 2006)	Total no. participants n=1039 (32 excluded, 22 drop-outs) True Acupuncture group n=326 Sham Acupuncture group n=365 Conventional	Parallel design. Randomised, controlled Patients were blinded to whether they received real acupuncture or sham acupuncture (however, 16 in the Treatment group and 17 in the Sham acupuncture group realised what treatment they	Yes	Treatment group: Needling on ST34, ST36, EX-LE4, SP9, SP10, GB34 with optional 1-4 Ashi points and 1-2 or 16 defined distal acupoints; plus 6 sessions physiotherapy and Diclofenac as-needed (no Diclofenac in Weeek 24-26). 10 sessions in 6 weeks Control groups: sham acupuncture group: 6 sessions physiotherapy plus(shallow puncture to non-acupuncture points) and Diclofenac as-needed	According to ACR 1995	Yes 515 adverse events were reported (179 in the treatment group, 177 in the sham acupuncture group and 159 in the conventional therapy group). The most frequently reported were arthralgia, bone pain, haematoma,	① WOMAC index ② SF-12 physical subscale ③ SF-12 mental subscale ④ Patient global assessment	① ② ④ the true acupuncture group had significantly greater to reduction in scores than the Conventional Therapy group. The sham acupuncture group had significantly greater reductions in ①, ②, and ④ compared with the Conventional Therapy group ($p < 0.0001$), but there was no statistical difference between True and Sham acupuncture groups ($p=0.48$)	3

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
	Therapy group n=316	received) 6 weeks treatment period, follow-up at week 26; no Diclofenac from week 24		Conventional Therapy group: 6 sessions of physiotherapy plus Diclofenac 150 mg/d or rofecoxib 25 mg/d		back pain and joint lock.		③ No statistical difference among three groups (in terms of change in SF-12 mental subscale)	
(Wu and Bao, 2008)	Total no. participants n=40 Treatment group n=20 Control group n=20 No information of dropouts.	Parallel design Randomised (randomly divided into two groups) but no information on procedure No information of blinding 1 month treatment period, no follow-up	No information	Treatment group: Needling on EX-LE2, EX-LE4, EX-LE5, SP9, SP10, SP11, ST34, ST36, Electro applied on EX-LE4, EX-LE5 and SP10, SP11. 3 sessions weekly for 4 weeks Control group: Diclofenac 25mg, t.i.d. for 1 month	According to ACR 1986	No information	① Lysholm scores	The Lysholm scores were significantly greater (higher score represents better clinical symptoms and functioning) after the treatment period in the Treatment group compared with the Control group ($p < 0.05$). Within groups analysis indicated that in both groups, there was a significant increase in the Lysholm score at the end of the study period compared with baseline ($p<0.01$)	1
(Tao and Lu, 2003)	Total of 116 knees Treatment group n=60 Control group n=56 No information of dropouts	Parallel design Randomised (randomly divided into two groups) but no information on procedure No information of blinding 1 session every other day (10 sessions total)	No information	Treatment group: Needling on CV4, CV12, ST12, ST24, SP15, and abdominal extra points, accompanied by warming needling on ST35, EX-LE2, Ex-LE4, GB33, GB34, plus leg lift exercises Control group: Warming needling on ST35, EX-LE2, EX-LE 4, GB33, GB34 with optional needling of additional acupoints (no exercise)	Inclusion criteria according to ACR (didn't mention the particular year), no exclusion criteria	No information	Researchers created their own Index based on symptoms and knee function	With groups analysis indicated that in both groups, the Index score was significantly lower at the end of the treatment period compared with baseline (lower score represents a more favourable outcome) ($p < 0.01$); Between groups analysis indicated that the decreased in Index score was significantly greater in the Treatment group compared with the Control group ($p<0.05$)	1

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Li and Zhu, 2008)	Total no. participants n=60 participants (104 knees) Treatment group n=30 (54 knees) Control group n=30 (50 knees) No information of dropouts	Parallel design Randomised (randomly divided into two groups) but no information on randomisation procedure Single blind study 1 session everyday (10 sessions in total)	No information	Treatment group: Needling on ST34, ST35, ST36, EX-LE4, SP9, GB34 and Ashi points, electro acupuncture applied, plus moxibustion on CV8 (moxa box) 1 session everyday for 10 sessions Control group: Same as treatment group except sham moxibustion applied Sham moxibustion = applied tin foil and asbestos sheet between the skin and the moxa to prevent heat reaching skin)	According to ACR 1995	No information	① Pain VAS ② Functional score of knee (function)	Within groups analysis indicated that ① ② scores were significantly increased (better clinical functions) after the treatment compared with baseline for both groups (p <0.01). Between groups analysis demonstrated significantly greater improvements in ① and ② scores in the treatment group compared with the Control group (p<0.01), but there no statistically significant difference in pain VAS between groups at 1 month follow-up.	1
(Lao and Deng, 2003)	Total no. participants n=138 Treatment group n=85 Control group n=53 No information of dropouts	Parallel design Randomisation (randomly divided into two groups) No blinding description 1 month treatment period, assessment at 1 month follow-up	No information	Treatment group: Warming needling on SP9, SP10, ST34, ST36, EX-LE4, EX-LE5 & distal points according to TCM Syndrome Differentiation, then applied electro-stimulation (no information of which acupoints applied with electro). Also oral herbal medicine (modified Du Huo Ji Sheng Tang), 3 bags per week for 4 weeks 1 session everyday, 10 sessions total Control group: Indomethacin 25mg t.i.d. and Diclofenac 500mg b.i.d. for 1 month	According to criteria recommended by the medical committee of Chinese People Liberation Army	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function, referred to ACR criteria)	① There was a significant difference between groups after treatment (p <0.01), with clinical efficacy higher in the treatment group that the control group	1
(Wu, 1998)	Total no. participants n=70 Treatment group n=35 Control group n=35 No information of dropouts	Parallel design Randomisation No information of blinding No definition of treatment period & follow-up	No information	Treatment group: Electro needling on EX-LE2, EX-LE4, GB34, SP9, ST34, ST36 and Ashi points + massage on the knee + physio + physical exercise 1 session everyday Control group: same as the Treatment group except for physical exercise	Author defined inclusion criteria but no reference, no exclusion criteria	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function, no reference given)	① Clinical Efficacy in the Treatment group was significantly higher in the Treatment group compared with the Control group after treatment (p <0.05)	1

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Song et al., 2001)	Total n=122 (148 knees) Warming Acupuncture plus TDP group n=33 (39 knees) Acupuncture plus TDP group n=35 (38 knees) TDP group n=28 (33 knees) Diclofenac group n=26 (38 knees) No information of dropouts	Parallel design Randomisation (randomly divided into two groups) No information of blinding No description of treatment period, 1 month follow-up	No information	Treatment group: Warming needling on GB34, ST36, EX-LE2, EX-LE4, EX-LE5, SP10 plus herbal medicine TDP treatment (special electromagnetic spectrum lamp). No description of frequency and treatment period. Control groups: group 1: acupuncture plus TDP group 2: herbal medicine (TDP) only group 3: Diclofenac 300-600 mg bid for 1 week	According to ACR (didn't mention the version), no exclusion criteria	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function, no reference given)	① Significantly higher Clinical efficacy in the Treatment group compared with the other groups($p < 0.05$),	1
(Xi et al., 2008)	Total no. participants n=40 Laser acupuncture group n=20 (2 drop-outs) Control group n=20 (7 drop-outs)	Parallel design Randomised, controlled. Single-blind (reported that assessor blinded) 4 weeks treatment period, no follow-up	No information	Treatment group: 650 mm red laser and 10.6 μm CO_2 laser on ST35 3 sessions every week for 4 weeks Control group: 650 mm red laser and 10.6 μm CO_2 laser on fibular head 3 sessions every week for 4 weeks	ACR 1995	Yes. 3 cases of side effects reported in the treatment group	① Knee function scale (referred to Bellamy N et al. *J Rheumatol.* 1988;15(12):1833-1840.)	① Within groups analysis showed a significant reduction in Knee Function Score (equates to better outcome) in the treatment group after treatment ($p < 0.001$). Between groups analysis: no significant difference between the treatment group and the control group at end of treatment period	2
(Cai and Huang, 2004)	Total n=109 Treatment group n=41 Control group 1 n=36 in the control group 1 Control group 2 n=32 No information of dropouts	Parallel design No information of randomisation & blinding 10 days treatment period, no follow-up	No information	Treatment group: Needling on ST34, ST35, ST36, EX-LE4 and extra point with special manipulation with 1-2 optional points, plus TDP and cupping Control groups: Group 1: needling on ST35, ST36, SP9, GB34 and EX-LE4 plus TDP and cupping Group 2: Acupoint stimulation plaster (containing nano-materials i.e. nano-technology) on ST35 and Ashi.	ACR 1986	No information	① Clinical efficacy criteria (based on ranking of clinical symptoms and joint function; recommended by Shanghai Health Bureau, China, 1998)	① Significant difference between three groups ($p < 0.05$) (92.7% in the treatment group, 75.0% in the control group 1, and 65.6% in the control group 2)	0

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Zhang et al., 2004a)	Total no. participants n=50 Acupuncture group n=32 Control group n=18 No information of dropouts	Parallel design Randomisation (randomisation table used) & no information of blinding Treatment period varied between the study groups (42 days for treatment group, 21 days for control group) No follow-up	No information	Treatment group: Long needles punctured in ST35, EX-LE4, GB34 and SP9 1 session every other day, total 21 sessions Control group: Oral administration of Meloxicam 7.5mg qd. for 21 days	Author defined but no reference	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function referred to paper in Chinese literature)	① Significant difference between groups in favour of the treatment group ($p < 0.01$)	2
(Zhao, 2007)	Total no. participants n=60 No information of dropouts	Open label design 1 year follow-up No information of randomisation & blinding Treatment period: unclear	No information	Treatment group: Warming needling on EX-LE2, EX-LE4, ST35, ST36, SP9, GB33, GB34, GB37 and Ashi, plus external herbal medicine application and oral herbal patent medicine 30 sessions of acupuncture total 62 days of external herbal application No treatment period mentioned for oral medicine	ACR 1986	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function referred to paper in Chinese literature)	① Clinical efficacy was 91.67%.(no statistical analysis conducted)	0
(Bi, 2006)	Total no. participants n=120 Treatment group n=60 Control group n=60 No information of dropouts	Parallel design Randomisation (randomly divided into two groups) No information of description Treatment period varied between the treatment group and the ontrol group 2 years follow-up	No information	Treatment group: Needling on EX-LE4, ST34, ST36, GB34 with optional acupoints, plus herbal medicine ionotherapy 1 session everyday, 20 sessions total Control group Knee joint injection with dexamethasone 5mg, + Vic B1 50mg + triamcinolone acetonide 20mg 1 session every 15 days, 4 sessions total	ACR 1995	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function referred to paper in Chinese literature)	① No statistical significance between two groups, ($p > 0.05$) but significant difference in the rate of recurrence (less recurrence in the treatment group) ($p < 0.01$)	1

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Qiu et al., 2002)	Total no. participants n=64 Acupuncture group n=33 Control group n=31 No information of dropouts	Parallel design Randomisation (envelope method) No information of dropouts 2 weeks treatment period	No information	Treatment group: Needling around Ashi points (4-8 points around an Ashi points) plus EX-LE4, EX-LE5 and ST36, GB34, plus massage and exercise 1 session daily for 2 weeks Control group Massage and exercise only 1 session daily for 2 weeks	ACR 1996	No information	① Pain VAS ② Clinical efficacy (based on ranking of clinical symptoms and joint function, no reference)	① ② Within-groups analysis indicated a significant difference between two groups and within the treatment group, there was also a significant change from baseline ($p<0.05$)	2
(Jia et al., 2005)	Total n=120 Combination therapy group n=40 Acupuncture group n=40 Exercise group n=40 No information of dropouts	Parallel design Randomised (no detailed information of randomisation) No blinding 53 days treatment periods, 3 and 6 months follow-up	No information	Treatment group (Combination therapy): Needling on SP9, SP10, GB34, EX-LE4, EX-LE5, ST34, ST36, plus muscle exercise 1 session everyday, 45 sessions in total 2 Comparison groups: Acupuncture group: needling only Exercise group: exercise only 1 session everyday 45 sessions total	ACR (no publication year given)	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function, no reference) ② Recurrence rate in follow-up period	① ② Combination therapy was significantly superior to acupuncture only or exercise only ($p<0.01$) but there was no significant difference between acupuncture and exercise.	1
(Xu, 2008)	Total no. participants n=80 Combined therapy group n=20 Acupuncture group n=30 Warming needling group n=30 No information of dropouts	Parallel design Randomised (randomisation table being applied) No information of blinding Treatment period 15 weeks No follow-up mentioned.	No information	Treatment group (Combined Therapy group): Warming needling on EX-LE4, EX-LE5 and Ashi points, as well optional points, plus bleeding cupping 2 sessions weekly, 30 sessions total Comparison groups: group 1: needling only on the same acupoints group 2: needling plus moxibustion on the same acupoints. 2 sessions weekly, 30 sessions total	ACR 1995	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function referenced a paper in Chinese literature)	① The treatment group (combined therapy) results were significantly greater that the Acupuncture only group ($p<0.05$). No significant difference between the treatment group and warming needling group.	2

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Wang and He, 2007)	Total no. participants n=80 Combined therapy group n=40 Warming needling group n=40 No information of dropouts	Parallel design Randomised (randomisation table) No information of blinding Treatment period 40 days	No information	Treatment group (Combined therapy): Needling on EX-LE2, EX-LE4, ST35, GB33, GB34, SP10, ST34 plus TDP treatment 1 session every other day, 20 sessions in total Control group: Warming needling on EX-LE2, EX-LE4, ST35, GB33, GB34 and needling on SP10, ST34 1 session every other day, 20 sessions total	ACR 1986	No information	① Legnesne scale ② Clinical efficacy (based on the score change of the Legnesne scale)	① ② Within groups analysis demonstrated a significant change after treatment compared with baseline in both groups ($p<0.01$); between- groups analysis demonstrated that the changes in the treatment group were significantly greater than in the control group ($p<0.05$)	2
(Li et al., 2006)	Total no. participants n=120 Warming needling group n=60 (2 drop-outs) Needling group n=60 (4 drop-outs)	Parallel design Randomised (randomisation table) No information of blinding Treatment period 15 days overall No follow-up	No information	Treatment group: warming needling on GV4, GV6, EX-LE4, ST36, GB34 14 treatments in total (one treatment per day for 7 days then one day rest, than 1 treatment per day for another 7 days) Control group: Same acupoints as Treatment group but needling only Treatment protocol as above (14 treatments in total)	ACR 1991	No information	① Legnesne scale ② clinical efficacy (based on the score change on the Legnesne scale)	① ② The scores of Legnesne scale were significantly lower in the Treatment group compared to the Control group after treatment ($p <0.05$)	3
(Lin and Liang, 2005)	Total no. participants n=65 Treatment group n=35 Control group n=30 No information of dropouts	Parallel design Randomised (using procedure of drawing straws technique) No information of blinding Treatment period 40 days No follow-up	No information	Treatment group: Electro-warming needling on EX-LE4, ST35, GB34, SP9 1 session every other day, 20 sessions in total Control group: same acupoints but needling only 1 session every other day, 20 sessions total	ACR 1986	No information	① Clinical efficacy (based on ranking of clinical symptoms and joint function; referred to a paper in the Chinese literature)	① Treatment group associated with a significantly greater clinical efficacy following treatment compared with the Control group ($p<0.01$).	2
(Lin et al., 2004a)	Total no. participants n=80 Treatment group n=40	Parallel design Randomised (but no detailed information of randomisation) No information of	No information	Treatment group: Warming needling on EX-LE4, ST34, ST36, GB34 and optional points according to TCM syndrome differentiation 1 session everyday 30 sessions total	ACR 1995	No information	① Clinical efficacy (referred to Criteria of Diagnosis and Therapeutic Effect of Diseases and	① No significant difference between the two groups at the end of treatment phase ($p>0.05$) but the recurrence rate in the Treatment group was	1

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
	Control group n=40 No information of dropouts	blinding Treatment period varied with study group 1 year follow-up		Control group: Knee joint injection with Vitamin B12 0.5μg + triamcinolone acetonide 4mg and sodium hyaloroid 2ml 1 session weekly, 9 sessions total			Syndromes in Traditional Chinese Medicine, 1994, Government publication PR China)	significantly lower than the Control group (17.2% compared with 52%, p <0.01).	
(Wu et al., 2006b)	Total n=114 Treatment group n=60 Control group n=54 No information of dropouts	Parallel design Randomised (but no detailed information of randomisation) No information of blinding Treatment period 20 days	No information	Treatment group Warming needling on ST35, ST36, SP10, EX-LE2 1 session every day, 20 sessions total Control group Diclofenac tablet 75 mg qd. for 20 days	ACR (didn't mention which version)	No information	① Clinical efficacy (referred to a paper in the Chinese literature)	① The efficacy of the Treatment group was significantly higher than the Control group (p <0.01)	1
(Zhang et al., 2001)	Total n=60 Treatment group n=30 Control group n= 30 No information of dropouts.	Parallel design Randomised (but no detailed information of randomisation) No information of blinding	No information	Treatment group: warming needling on ST34, GB33, LI8 plus injection into Ashi points with combination of Vitamin B12, B1 and Chinese herbal medicine) 1 session every 3 days, 5 sessions total Control group: Diclofenac tablet 75 mg tid. for 17 days	No information inclusion and exclusion criteria	Yes, 5 adverse events reported in the control group, no adverse events in the treatment group	① Clinical efficacy (based on ranking of clinical symptoms and joint function, no reference given)	① Significantly greater efficacy in the Treatment group compared with the Control group(p<0.05). Within-groups analysis indicated a significant improvement within both groups at end of treatment compared with baseline.	1
(Sun et al., 2008)	Total n=56 (80 knees) Treatment group n=29 (41 knees) Control group n=27 (39 knees) No information of dropouts	Parallel design Randomised (randomisation table) No information of blinding Treatment period 20 days 2 months follow-up	No information	Treatment group: indirect moxibustion with aconite mat on 2-4 optional acupoints among EX-LE2, EX-LE4, ST34, ST35, SP9, SP10, GB34, BL18, BL23 1 session everyday, 20 sessions in total Control: Diclofenac tablet 75 mg qd. for 20 days	TCM diagnosis criteria (referred to Clinical Research Guidelines of New Chinese Medicine [China] 2002); No citation of Western medicine criteria	No information	① Symptoms and signs scale (referred to Clinical Research Guidelines of New Chinese Medicine ,China, 2002) ② Clinical efficacy (based on the score change of the symptoms and signs scale)	① Significant difference within the treatment (moxibustion) group after the treatment compared with baseline (p <0.01); and significant difference between groups in favour of the treatment group at the end of the treatment phase (p<0.05) ② No significant difference between the two groups at the end of treatment period, but at 2 months follow-up, clinical efficacy was significantly better in the treatment group compared with the control group (p<0.05).	2

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Li et al., 2008)	Total n=62 Treatment group n=31 (1 drop-out) Control group n=31 (1 drop-out)	Parallel design Randomised (odd numbers into one group, even numbers into the other) No information of blinding 4 weeks treatment period, no follow-up	No information	Treatment group: Indirect moxibustion with aconite mat on EX-LE4, ST35, 36 1 session everyday, 6 days per week, 24 sessions total Control: Xian Ling Gu Bao capsule (Chinese herbal patent medicine) 3 capsules, bid for 28 days	ACR 1995; TCM Syndrome Differentiation Criteria (referred to Clinical Research Guidelines of New Chinese Medicine ,China, 2002)	Yes, 1 adverse event report only in the control group	① Pain VAS ② Lequesne scores ③ Clinical efficacy (referred to Clinical Research Guidelines of New Chinese Medicine ,China, 2002)	① ② Significant difference between Treatment group and Control group on scores of Pain VAS and Lequesne after treatment (in favour of the Treatment group) ($p < 0.05$); within-groups analysis indicated significant change within both groups at the end of treatment compared with baseline($p < 0.01$) Between groups ③ No significant difference in clinical efficacy between the two groups.	3
(Fu et al., 2007)	Total no. participants n=34 No information of dropouts.	Open label design (no control group) No standard treatment period (from 20-40 days), no follow-up No information of randomisation or blinding	No information	Scarring moxibustion on sensitive Ashi points around the knee 1 session per day, 1-2 sessions total, the scar healing should take around 20 days;	ACR 1995; TCM Syndrome Differentiation (no reference given)	No information	① Knee function scores for the following: pain, walking, joint range of motion, unstable sensation, swelling, walking up and down stairs, knee locking (author created and referred to a Chinese publication)	① Within-groups analysis demonstrated a significant reduction in all Knee function scores (except for the knee lock score) after treatment compared with baseline ($p < 0.01$)	0
(Huang, 2002)	Total no. participants n=75 Treatment group n=50 Control group n=25 No information of dropouts	Parallel design No standard treatment period (around 28-37 days), No information of blinding and no follow-up	No information	Treatment group: scarring moxibustion on ST36 and GB39 1 course of moxa treatment only = moxa applied, then blister occurred 3-7 days later then scar healing occurred in 25-30 days Control group: electro-acupuncture on ST34, ST36, EX-LE4, EX-LE5, SP10, BL40 1 session every day for the same treatment period as the treatment group (no exact detail recorded).	ACR 1995, but no exclusion criteria description	No information	① Clinical efficacy (based on the ranking of the symptoms and signs, no reference given)	① Significant difference between groups ($p < 0.01$):, efficacy of Treatment group 92%,, Control group 60%.	0

Ref	Sample size and No. of dropouts	Study design	Power calculation	Study intervention /control treatment)	Diagnostic criteria	Safety monitoring	Outcome assessment	Results	Jadad Scores
(Li et al., 2002)	Total n=50 Treatment group n=25 Control group n=25 No information of dropouts	Parallel design Randomised (randomisation table applied) No information of blinding 20 days treatment period, no follow-up	No information	Treatment group: moxibustion on GV3 and ST35, plus isotonic and isometric exercises for the lower limbs 1 session per day, 20 sessions in total Control group: infrared physiotherapy plus knee joint massage 1 session per day, 20 sessions total	ACR 1983, but no exclusion criteria description	No information	① Lysholm scores	① Significant improvement in the pain relief and the stability of the knee joint in the Treatment group compared with the Control group ($p < 0.05$). No significant difference between groups in the motion range of the knee and climbing stairs function ($p > 0.05$).	2
(Le, 2001)	Total n=120 treatment group n=40 control group n=40 No information of dropouts	Parallel design Randomisation (no detailed information of randomisation) No information of blinding 20 days treatment period, no follow-up	No information	Treatment group: Moxibustion apparatus plus needling on SP10, ST34, EX-LE4, EX-LE5. 1 session every day, 20 sessions in total Control Group 1: warming needling on ST34, SP10 and EX-LE4, EX-LE5 1 session every day, 20 sessions in total Control Group 2: electro-acupuncture on the same points as above 1 session every day, 20 sessions in total	Diagnostic criteria according to a Chinese literature, no information of exclusion criteria	No information	① Clinical efficacy (referred to a paper in the Chinese literature)	① No significant difference between the Treatment group and the Control group 1 ($p > 0.05$);. Significantly greater clinical efficacy in the Treatment group compared with Control group 2 ($p < 0.05$) .2)	1
(Gu and Xu, 2008)	Total no. participants n=60 Treatment group n=30 Control group n= 30 No information of dropouts.	Parallel design Randomisation (no detailed information of randomisation) No information of blinding 20 days treatment period, no follow-up	No information	Treatment group: Warming needling on EX-LE4, 5, GB34, SP9, ST36, BL40, plus cupping 1 session everyday, 20 sessions total Control group: The same as the treatment group except for exclusion of BL40 (no treatment on BL40)	Diagnosis criteria (no reference); TCM criteria of Syndrome Differentiation (no reference given)	No information	① Clinical efficacy (no reference) ② Onset time for pain relief	① No significant difference between groups ② Treatment group associated with a significantly shorter onset time for pain relief (11.80±3.65 days) in comparison to Control group (16.63±3.97 days) ($p < 0.05$).	1

Key: TDP – acronym of a medical device according its Chinese name, Te Dian Po (Te Ding Dian Ci Po Pu) a special electromagnetic spectrum lamp; ACR - American College of Rheumatology

Table 5.4 Published studies of acupuncture treatment for OA met the modified CONSORT criteria of nonpharmacologic treatment

Item	Ref. (Berman et al., 1999)	Ref. (Sangdee et al., 2002)	Ref. (Berman et al., 2004)	Ref. (Witt et al., 2005)	Ref. (Vas et al., 2006)	Ref. (Scharf et al., 2006)	Ref. (Wu and Bao, 2008)	Ref. (Tao and Lu, 2003)	Ref. (Li and Zhu, 2008)	Ref. (Lao and Deng, 2003)	Ref. (Wu, 1998)	Ref. (Song et al., 2001)	Ref. (Xi et al., 2008)
1	√	√	√	√	√	√	√	√	√	√	×	√	√
2	√	√	√	√	√	√	√	√	√	√	√	√	√
3	√	√	√	√	√	√	√	√	√	√	√	√	√
4	√	√	√	√	√	√	√	√	√	√	√	√	√
4A	√	√	√	√	√	√	√	√	√	√	√	√	√
4B	√	√	√	√	×	√	×	×	×	×	×	×	√
4C	×	×	√	×	×	√	×	×	×	×	×	×	×
5	√	√	√	√	√	√	√	√	√	√	×	√	√
6	√	√	√	√	√	√	√	√	√	√	√	√	√
7	√	×	√	√	√	√	×	×	×	×	×	×	×
8	√	×	√	×	√	√	×	×	×	×	×	×	√
9	×	×	√	×	√	×	×	×	×	×	×	×	√
10	×	×	√	×	×	×	×	×	×	×	×	×	√
11A	√	√	√	√	√	√	×	×	×	×	×	×	√
11B	×	×	√	√	√	√	×	×	×	×	×	×	√
12	√	√	√	√	√	√	×	×	√	×	×	×	√
13	√	√	√	√	√	√	×	×	×	×	×	×	×
New	×	×	√	√	×	√	×	×	×	×	×	×	×
14	×	×	√	√	×	√	√	√	×	×	×	×	√
15	√	√	√	√	√	√	√	√	√	√	√	√	√
16	√	√	√	√	√	√	×	×	×	×	×	×	×
17	√	√	√	√	√	√	√	√	√	√	√	√	√
18	×	×	√	√	√	√	×	×	×	×	×	×	×
19	√	√	√	√	×	√	×	×	×	×	×	×	√
20	√	√	√	√	√	√	√	√	√	√	√	√	√
21	√	√	√	√	√	√	×	×	×	×	×	×	√
22	√	√	√	√	√	√	√	×	×	×	×	×	×

Table 5.4 Continued

Item	Ref. (Cai and Huang, 2004)	Ref. (Zhang et al., 2004a)	Ref. (Zhao, 2007)	Ref. (Bi, 2006)	Ref. (Qiu et al., 2002)	Ref. (Jia et al., 2005)	Ref. (Xu, 2008)	Ref. (Wang and He, 2007)	Ref. (Li et al., 2006)	Ref. (Lin and Liang, 2005)	Ref. (Lin et al., 2004a)	Ref. (Wu et al., 2006b)	Ref. (Zhang et al., 2001)
1	×	√	×	×	√	√	√	√	√	√	√	√	×
2	×	√	√	×	√	√	×	√	√	√	√	√	×
3	√	√	√	√	√	√	√	√	√	√	√	√	√
4	√	√	√	√	√	√	√	√	√	√	√	√	√
4A	√	√	√	√	√	√	√	√	√	√	√	√	√
4B	×	×	×	×	×	×	×	×	×	×	×	×	×
4C	×	×	×	×	×	×	×	×	×	×	×	×	×
5	×	√	×	×	×	×	×	√	√	√	√	√	√
6	√	√	√	√	√	√	√	√	√	√	√	√	√
7	×	×	×	×	×	×	×	×	×	×	×	×	×
8	×	√	×	×	×	√	×	√	√	√	×	×	×
9	×	×	×	×	×	×	×	×	×	×	×	×	×
10	×	×	×	×	×	×	×	×	×	×	×	×	×
11A	×	×	×	×	×	√	×	×	×	×	×	×	×
11B	×	×	×	×	×	×	×	×	×	×	×	×	×
12	×	×	×	×	√	√	×	√	√	×	×	×	×
13	×	×	×	×	×	×	×	×	√	×	×	×	×
New	×	×	×	×	×	×	×	×	√	×	×	×	×
14	×	×	√	×	×	×	×	×	×	×	√	×	×
15	√	√	√	√	√	√	√	√	√	√	√	√	√
16	×	×	×	×	×	×	×	×	×	×	×	√	×
17	√	√	√	√	√	√	√	√	√	√	√	√	√
18	×	×	×	×	×	×	×	×	×	×	×	×	×
19	×	×	×	×	×	×	×	×	×	×	×	×	×
20	√	√	√	√	√	√	√	√	√	√	√	√	√
21	×	×	×	×	×	×	×	×	×	×	×	×	×
22	×	×	×	×	√	√	×	×	×	√	×	×	×

Table 5.4 Continued

Item	Ref. (Sun et al., 2008)	Ref. (Li et al., 2008)	Ref. (Fu et al., 2007)	Ref. (Huang, 2002)	Ref. (Li et al., 2002)	Ref. (Le, 2001)	Ref. (Gu and Xu, 2008)
1	√	×	×	×	√	×	√
2	√	√	√	√	√	×	√
3	√	√	√	√	√	√	√
4	√	√	√	√	√	√	√
4A	√	√	√	√	√	√	√
4B	×	×	×	×	×	×	×
4C	×	×	×	×	×	×	×
5	√	√	√	×	√	√	√
6	√	√	√	√	√	√	√
7	×	×	×	×	×	×	×
8	√	√	×	×	√	×	×
9	×	×	×	×	×	×	×
10	×	×	×	×	×	×	×
11A	×	×	×	×	×	×	×
11B	×	×	×	×	×	×	×
12	√	√	×	×	√	×	√
13	×	×	×	×	×	×	×
New	×	×	×	×	×	×	×
14	√	√	×	√	×	×	√
15	√	√	√	√	√	×	×
16	×	×	×	×	×	×	×
17	√	√	√	√	√	√	√
18	×	×	×	×	×	×	×
19	×	√	×	×	×	×	×
20	√	√	√	√	√	√	√
21	×	×	×	×	×	×	×
22	×	×	×	×	×	×	×

Chapter 6 Reliability of the Chinese Medicine Diagnostic System

6.1. Introduction

In clinical research, scientific research methodology demands that the measurement of clinical outcome variables be reliable or consistent. Reliability or reproducibility refers to the ability of a test or experiment to be accurately reproduced or replicated. Within a research context, the measurement of the degree of agreement between observers conducting the same measurement is called 'inter-rater reliability'(Valentin et al., 2002) 'Intra-rater reliability' or 'test-retest reliability' refers to the degree of agreement when the same observer repeats the observation.(Valentin et al., 2002) Chinese medicine (CM) has its own diagnostic variables that are used as evidence of change in a patient by CM practitioners. CM diagnostic variables include symptoms and signs which are used to determine the disease and the Syndrome of a disease or disorder. It could be argued that if CM diagnostic variables are consistent, then these could be used in clinical trials of CM as outcome variables in addition to western medicine outcome variables to assess the efficacy of CM therapies.

There are very few studies which have investigated the consistency of CM diagnostic variables, like tongue diagnosis (Kim et al., 2008, O'Brien et al., 2009b) and pulse diagnosis.(King et al., 2002, O'Brien et al., 2009b) Several studies have also investigated the consistency of CM Syndrome diagnoses in certain diseases like irritable bowel syndrome, low back pain, headaches, rheumatoid arthritis and hypercholesterolemia.(Sung et al., 2004, MacPherson et al., 2004, Hogeboom et al., 2001, Birch and Sherman, 1999, Coeytaux et al., 2006, Zhang et al., 2005a, O'Brien et al., 2009a)

In rheumatology, Zhang and colleagues have tried to ascertain the reliability of CM Syndrome diagnosis in rheumatoid arthritis.(Zhang et al., 2004b, Zhang et al., 2005a, Zhang et al., 2008a) There have been no studies in osteoarthritis (OA) however. Although three CM Syndromes of OA have been identified in the Chinese official guideline on diagnosis and criteria of clinical effectiveness,(The State Administration of Traditional Chinese Medicine, 1994) there are no empirical studies of the CM Syndromes of OA. Therefore we do not know how many Syndromes of OA actually exist nor whether CM Syndrome diagnosis in OA is reliable.

It is important to investigate the reliability of CM diagnoses in OA for three reasons. Firstly, in general if diagnosis is reliable there can be greater confidence that correct treatment is being received. Secondly, if CM diagnostic variables are found to be reliable, then there is justification for using these as outcome variables in clinical trials. Thirdly, it is important to establish empirically the CM Syndromes of OA since treatment follows diagnosis. This chapter will give an overview of the current knowledge with respect to reliability of CM diagnosis.

6.2 Reliability of Chinese medicine diagnostic methods

CM differs from the conventional medicine in a number of ways, including the diagnostic methods used. CM diagnostic approaches rely more on the clinician's interpretation of the patient's symptoms and signs rather than on laboratory tests.(Zhang et al., 2003) The process of CM diagnosis is the collection of patient information through taking a case history and an overall observation of symptoms and signs, analysis of these according to CM theories and drawing a conclusion about the disease and CM Syndrome.(Deng et al., 1984, Maciocia, 2004) As discussed previously, there are four diagnostic methods used in CM diagnosis: Inquiry, Inspection, Auscultation/Olfaction, and Palpation.

Up to now, only one study has investigated the reliability of the CM diagnostic process in a comprehensive way at both the level of data collection (using three of the four diagnostic methods, Palpation, Inspection and Auscultation) and data analysis or Syndrome differentiation (diagnosis using the Eight Guiding Principles and Zang-Fu Theory).(O'Brien et al., 2009a, O'Brien et al., 2009b) Other studies have focussed on the consistency of individual diagnostic methods such as pulse diagnosis or tongue diagnosis or on the CM Syndrome diagnosis only.

This section will summarise the current knowledge about the reliability of the four diagnostic methods, and CM Syndrome diagnosis according to the Eight Guiding Principles and Zang-Fu Theory.

6.2.1 Inspection

Only one comprehensive inter-rater reliability study has assessed the reliability of various aspects of visual inspection in a CM examination.(O'Brien et al., 2009b) In this study, diagnostic variables of inspection included spirit (shen), complexion,

colour around the eye, hair, tongue body and tongue coating. The researchers found various level of agreement amongst the three practitioners, from slight ($0.00 < \kappa \leq 0.20$) in the case of colour around the eye and skin texture, to fair ($0.21 < \kappa \leq 0.40$) for colour of complexion, to almost perfect agreement ($0.81 < \kappa \leq 1.00$) in the case of presence of shen. The Kappa value (κ) is a measure of the level of agreement between observers beyond that occurring by chance. When comparing between *at least* two practitioners, the level of agreement for most of diagnostic outcomes of inspection was higher. For example, the level of agreement for colour of complexion was 93% ($\kappa = 0.85$) The relatively low levels of agreement for many of the inspection variables may be due to a more subtle level of observation required, and also demonstrates the subjectivity of inspection. (O'Brien et al., 2009b)

There are some inherent difficulties in measuring reliability of inspection. Firstly, the quantification of subjective judgements made by the practitioner is not easy. For example judgement of a patient's spirit is part of Inspection, however it is hard to quantify someone's spirit which depends on the physical health status and may change with emotional state. Secondly, descriptions of particular observation indices in CM have not been defined clearly, leading to difficulties in quantifying or measuring such items. For example, in observing the colour of the complexion, five colours (green, red, yellow, white and black) are typically described in CM texts (Deng et al., 1984), and attempts may be made to describe these further in terms of depth of colour (eg. light, dark and deep). However, the eye is able to detect dimensions such as hue, saturation and brightness. Describing the complexion in terms of five colours is limited. The inherent subjectivity of inspection may lead to low inter-rater reliability among CM practitioners.

In China, some medical instruments and computerised image analysis systems have been developed and introduced into analysis of CM tongue diagnosis.(Chen and Zhang, 2008, Wang et al., 2005, Wei et al., 2002, Weng and Huang, 2001) Most of them adopt the red/green/blue (RGB) colour model in which red, green, and blue light are added together in various combinations to reproduce a broad array of colours. Several other models have been applied in tongue research.(Gong et al., 2005, Wei and Li, 1995, Zhang et al., 2005b, Zhang et al., 2004d, Xu et al., 1993, Zhang et al., 2005d), including the 'Lab' model (a colour-opponent space with three dimensions,

dimension L for lightness and dimensions a and b designating the colour-opponent dimensions), the YUV model (Y designating the luminosity or brightness component and U and V the chromaticity or colour components), and the HSL (hue/saturation/lightness) model which attempts to describe perceptual colour relationships more accurately than the RGB and the Hue model. These models are attempts to quantify characteristics of the tongue body and tongue coating colour. Although studies have found that tongue colour identification systems can reflect the characteristics of tongue colour and record similar judgements as those of CM practitioners, there are several factors which could contribute to errors in measurement, such as the shape of tongue, the structure of curved surface and the sampling area.(Wang et al., 2005, Wei et al., 2002, Weng and Huang, 2001)

There are very few studies of the reliability of tongue inspection in English language publications.(Kim et al., 2008, O'Brien et al., 2009b, Rupp, 1998) Two of the studies utilised slides and one utilised real patients.(O'Brien et al., 2009b) One study of the inter-reliability and intra-reliability of CM tongue inspection was conducted among thirty CM practitioners, most of whom were trained in Australia with a minimum of three years of CM education and a minimum of six months independent clinical experience.(Kim et al., 2008) The practitioners completed two questionnaires based on standard colour slides and test tongue slides. The standard colour slides (five colours: dark red, pale pink, pink, red, and purple) were scanned from a standard colour chart while ten tongue photographs were selected according to different diagnostic characteristics. The findings indicated poor reliability for CM tongue inspection. The study also suggested that the low levels of inter- and intra-practitioner agreements may be due to ambiguous operational definitions of tongue colour characteristics in CM, and were not related to duration of clinical practice. There are limitations of using slides of tongues compared with real tongue presentations since qualities such as moisture may not be readily detectable in slides. The actual tongue diagnosis (like other CM diagnostic techniques) is also dependent on the experience of the CM practitioner.

O’Brien and colleagues conducted an inter-rater reliability of CM diagnosis that included tongue diagnosis as a substudy of a clinical trial investigating the efficacy of Chinese herbal medicine in the treatment for hypercholesterolemia. They reported a

'slight' level of agreement ($0.00 < \kappa < 0.20$) in terms of tongue body characteristics (size, colour, presence of teeth marks and papillae) and a 'fair' level of agreement ($0.21 < \kappa < 0.40$) in terms of tongue coating characteristics (including quality, colour and thickness) amongst three CM practitioners (all of whom had at least five years experience).(O'Brien et al., 2009b). This suggests that tongue diagnosis is quite subjective and that some aspects are relatively reliable, and others not so reliable.

6.2.2 Auscultation/Olfaction

In CM clinical practice, not much significance is attached to Auscultation since the hearing ability of practitioners varies from person to person. In ancient China, there was no effective tool to capture sound information, thus as a diagnostic tool it has not developed particularly. In contrast, in conventional medicine, auscultation has become an effective way to distinguish pathological changes in the chest since the invention of stethoscope.

In CM, the intensity of voice is used to identify 'deficiency' or 'full' ('excess') Syndromes and the relevant zang-fu organs which may be involved in the Syndrome. For example, a very loud, barking cough typically indicates a 'full' Syndrome. In addition, according to CM theory, sounds also correspond to the Five Element Theory. For example, shouting is associated with Wood, laughing with Fire, singing with Earth, crying with Metal and groaning with Water.(Maciocia, 2005) But this theory has not been verified using scientific research methods.

Some research has attempted to quantify and interpret the voice using a spectrogram.(Mo et al., 1998b) One study (Mo et al., 1998a) demonstrated there were significant differences in vowel pronunciation of Mandarin words and cough sounds measured by a sound spectrogram amongst a group of healthy people and three groups of patients with cough (Deficiency of Lung Qi group, Deficiency of Lung Yin group and Full Syndrome group). The author argued that CM auscultation can be objectified by measuring the sound spectrum values of the voice including harmonic waves, crest waves, amplitude, formant, noise, radical frequency and duration of the crest wave.(Mo et al., 1998a)

Only one study published in English has assessed the inter-rater reliability of auscultation variables in a CM examination. They found 'almost perfect' agreement

for voice strength and breath sounds between at least two CM practitioners.(O'Brien et al., 2009b) However, auscultation also includes eructation and other sounds such as groaning and crying which have not been studied with respect to reliability.

6.2.3 Inquiry

In conventional medicine, the consultation between the doctor and patient is the first and essential procedure in diagnosis. In CM, this is even more important since there is less reliance on objective medical diagnostic tests (as are used in orthodox medicine).(Lu et al., 2005) As the majority of information acquired from the Inquiry component of the CM examination are subjective symptoms, it is common to find inconsistency in diagnostic assessments among different doctors when subjective judgments are involved even in conventional medicine.(Moyer et al., 2000, Santucci et al., 2000)

Subjective symptoms are usually regarded as the subjective reaction to pathological changes in the human body and may also be used as a means of subjective assessment by the patient of the effectiveness of treatment. For example, low back pain or perspiration won't influence the diagnosis or categorisation of a hepatitis patient in conventional medicine; any change of defecation in the hepatitis patient after treatment won't determine the treatment strategy either. However, the above-mentioned information is important information in CM Inquiry and may result in a different Syndrome diagnosis and consequently different treatment plan. Zhang and colleagues argued that inquiry as a diagnostic method is not a valid instrument, because of the low level agreement of diagnosis amongst three practitioners in the diagnosis for rheumatoid arthritis patients.(Zhang et al., 2005a, Zhang et al., 2004b)

Research has found the use of relatively objective questionnaires to collect clinical data instead of simply recording notes during the taking of a case history could improve the agreement in CM diagnosis among CM practitioners for rheumatoid arthritis.(Zhang et al., 2008a) Another validation study also suggested a questionnaire designed to evaluate Yin deficiency Syndrome can help make CM diagnosis more objective and reliable in the diagnosis of that particular Syndrome.(Lee et al., 2007) In addition, another study recommended that multiple consultations could improve the agreement rates amongst different CM practitioners- repeated consultations and modification of treatment plans are common practices in CM and multiple

consultations can help in formulating the most appropriate diagnosis, treatment principle and regime.(Sung et al., 2004)

6.2.4 Palpation

Palpation in CM includes palpation of body parts as necessary, and taking the radial pulse- pulse diagnosis. Pulse diagnosis is a unique diagnostic technique of CM involving palpation of the pulse located at the radial artery on both wrists, assessing the characteristics of the pulse and interpreting these in relation to the functional and physiological state of the internal organs. In spite of its crucial role in the diagnostic process in CM, it is difficult to objectify and standardize pulse diagnosis. Some attempts have been made in China to try to objectify pulse diagnosis through development of pulse measuring apparatus.(Cai et al., 2007, Yang et al., 2000) However, some have argued that Zang-Fu Organ Theory and the principles of Syndrome differentiation have been ignored in the design of these machines, which are simply pulse tracing devices based on anatomy and physiology as described in conventional medicine.(Tian and Lu, 2008) In addition, the concept of Qi should be considered in the development of pulse measuring devices and used in research. In CM the pulse may change according to several factors including seasonal changes, diurnal variation, emotional state, physical health and even body fat distribution. That is, such changes are typically reflected in the pulse. Therefore, pulse diagnosis cannot be simplified as merely detecting the indexes of hydrodynamics.(Li, 2003b)

A study by Craddock (Craddock, 1997) found low levels of inter-rater and intra-rater reliability when increased complexity of pulse qualities were measured. Another study of the reliability of pulse diagnosis which standardised the pulse-taking procedures and definitions of the characteristics of each pulse showed a relatively high level of agreement between two independent pulse assessors in the first collection session in 66 subjects (81% agreement) and in the replicated session in 30 subjects two months later (80% agreement).(King et al., 2002) O'Brien and colleagues found a 'fair' level of agreement ($\kappa = 0.29$) among three practitioners in term of pulse force. (O'Brien et al., 2009b) However, variable findings have been reported in other studies. A review of published and unpublished reliability studies of pulse diagnosis (O'Brien and Birch, 2009) indicates that the reliability varies from a low level to a very good agreement. However caution should be taken in

interpretation of those findings because different approaches have been used to collect, analyse and report the data. For example, in one study CM students were used as raters; a low level of agreement was found at the beginning of formal pulse diagnosis teaching classes (week 1), at the conclusion of pulse teaching (week 14), and one year later.(Walsh et al., 2001) It could be argued that lack of clinical experience may reduce the possibility of agreement.

Current research indicates that unambiguous definitions of pulse characteristics is critical in pulse research.(King et al., 2006, O'Brien and Birch, 2009) Standardising the pressure applied (that is, measurement of finger strength) in pulse detection is the most difficult part in pulse research. (Tian and Lu, 2008) However, the integration of an ultrasound technique into a pulse detection device that could generate multi-dimensional tomograms of the pulse could be a new direction of pulse research.(Liu, 2003)

6.3 Reliability of the Eight Guiding Principles

The Eight Guiding Principles are the theoretical basis of CM Syndrome differentiation in the process of CM diagnosis. As explained in Chapter 2, the Eight Principles refer to four pairs of characteristics that describe the nature and location of disharmony in the body: Interior/Exterior, Deficiency/Excess, Cold/Hot and Yin/Yang.(Deng et al., 1984) The identification of patterns according to the Eight Guiding Principles can be regarded as the preliminary analysis or summary of the information collected through the four diagnostic methods.

There are very few studies have assessed the reliability of the Eight Guiding Principles. A study of the inter-rater reliability of TCM diagnosis of chronic low back pain,(Hogeboom et al., 2001) which evaluated the importance of the Eight Principles in diagnosis by six acupuncturists, found the Principles were only useful for 50% of patients in 25 diagnosis sessions, especially for the diagnosis of Excess or Deficiency. The study indicated that the diagnosis was related more to the practitioner’s habits, regardless of who the patient was.(Hogeboom et al., 2001) However, no statistical analysis was conducted and there were few (six) patients involved in this study. Therefore, care should be taken with interpretation of these results.

Another inter-rater reliability study of diagnosis according to the Eight Guiding Principles in 45 hypercholesterolemic patients (O'Brien et al., 2009a) found a reasonably good level of agreement (>80%) between at least two practitioners on the four pairs of principles, especially in the location of the disorder (Interior/Exterior). When considering the agreement amongst all three practitioners involved in the study, the level of agreement on the Eight Guiding Principles was lower, particularly for the nature of the disorder (Excess/Deficiency) (only 24%). As for the usefulness and the reliability of the Eight Guiding Principles in clinical diagnosis, further studies are needed in a range of conditions.

6.4 Reliability of Syndrome Differentiation

CM Syndromes can be diagnosed according to different theories, for example Zang-Fu Theory, Meridian Theory, Triple Jiao Theory, and Theory of Qi, Blood and Body Fluids.(Deng et al., 1984) Syndrome Differentiation according to Zang-Fu Theory is the most important method of diagnosing internal diseases in modern CM practice, and is widely used in everyday clinical practice.

As for the reliability of CM Syndrome diagnosis, only a handful of studies have investigated this. O'Brien and colleagues showed very good agreement (88%) between at least two practitioners on the pattern of 'Deficiency of Spleen Qi' in hypercholesterolemic patients though the level of agreement was only 24% between all three practitioners, and there was very little agreement on any other Syndrome. The overall poor reliability of CM Syndrome diagnosis might have been because the practitioners were required to formulate their own CM Syndrome diagnosis rather than choose a syndrome from a pre-selected list of Syndromes.(O'Brien et al., 2009a)

Other studies have also reported a low level of consistency of Syndrome diagnosis in other diseases, such as low back pain, irritable bowel syndrome, headaches, and rheumatoid arthritis.(Birch and Sherman, 1999, Sung et al., 2004, Coeytaux et al., 2006, Zhang et al., 2005a, Hogeboom et al., 2001) Results are set out in Table 6.1. Hogeboom and colleagues (Hogeboom et al., 2001) evaluated the inter-rater reliability of six CM acupuncturists who made diagnoses and treatment prescriptions for the same six patients with chronic low back pain on the same day. They found that diagnoses and treatments were dependent more on the practitioner than on the patient, and the low concordance amongst practitioners may be due to variation in CM

training of acupuncturists and the open structure of the patient evaluation procedure which did not ask the practitioners to choose from the pre-determined Syndromes. (Hogeboom et al., 2001) The similar low level of reliability in CM Syndrome diagnosis and acupoints selection was also observed in a headache study.(Coeytaux et al., 2006)

In addition, although some studies (Sung et al., 2004, Zhang et al., 2005a) used a Syndromes list recommended by the textbooks, they still found a low level of mean agreement between CM practitioners for CM Syndrome diagnosis and treatment principles. A fundamental issue with respect to generating lists of CM Syndromes is that the literature is not always clear with respect to Syndromes: for example, a literature study (Birch and Sherman, 1999) also showed there were 24 diagnostic patterns of low back pain described in 16 acupuncture books and substantial variation amongst books in recommended acupoints as well.

However, inter-rater reliability of CM diagnosis may be improved through a training process. (Zhang et al., 2008a, Schnyer et al., 2005, Mist et al., 2009) MacPherson and colleagues (MacPherson et al., 2004) reported that diagnostic concordance of low back pain amongst five practitioners was reasonable in terms of the percentage of congruent classifications (47-75% for primary Syndromes and 56-80% for secondary Syndromes), based on three pre-defined Syndromes. They conducted a series of meetings in which they shared their personal experience to develop the Syndromes shortlist and standardise the definitions of the Syndromes in a booklet (including the signs and symptoms characterising them). Zhang and colleagues (Zhang et al., 2008a) and Sung and colleagues (Sung et al., 2004) also demonstrated that a training exercise to obtain consensus on CM diagnostic criteria can lead to a higher agreement of CM diagnosis on patients with rheumatoid arthritis.

Various assessment forms and questionnaires have been developed to standardise and clarify CM terms and collect clinical data (Lee et al., 2007, Mist et al., 2009, Schnyer et al., 2005, O'Brien et al., 2009a). In China, researchers tried to establish scales for each individual Syndrome diagnosis.(Lu et al., 2006, Liu et al., 2006b, Wang et al., 2009, Zhou et al., 2006b) Lu and colleagues developed a scale for diagnosis of ‘Deficiency of Kidney Yang’ that they applied in 300 patients, which was based on a ranking score of 40 items, including urination, defecation, sexual motivation,

complexion colour, cold sensation, taste in the mouth, limbs movement, headaches, pulse and tongue appearance.(Lu et al., 2006) They reported that the consistency of the scale was good (Cronbach's $\alpha = 0.9835$) and that the results were reliable between two doctors for some patients ($\kappa = 0.815$), however there is a lack of detailed information reported in this study (Lu et al., 2006) Another study on Syndrome diagnosis of 'Liver Fire Flaring Upward' and 'Ascendant Hyperactivity of Liver Yang', showed a satisfactory internal consistency of the scale (Cronbach's $\alpha = 0.805$).(Liu et al., 2006b) The test-retest reliability between two doctors in the diagnosis of 'Syndrome of Liver Fire Flaring Upward' showed the correlation coefficient was 0.706 for patients with mild symptoms and 0.897 with severe symptoms. For the 'Syndrome of Ascendant Hyperactivity of Liver Yang' the correlation coefficient was 0.807 for mild patients and 0.834 for severe patients (Liu et al., 2006b) There were also similar results reported in studies on diagnosis in stroke patients with spastic paralysis and cervical spondylotic radiculopathy.(Wang et al., 2009, Zhou et al., 2006b) However, the methods used in those studies have not been reported clearly, making them difficult to to interpret.

Since many diseases/disorders share common CM Syndromes and one disease/disorder typically has several different Syndromes (according CM theory), it could be argued that development of a Syndrome diagnosis scale to standardise CM diagnosis that is applicable to real clinical practice is not easy. Standardising the examination techniques and increasing the number of observations may be effective ways to improve the accuracy and reliability of the physical examination. Further research is required in different diseases.

Fixed lists of Syndromes may be useful in some diseases and also can increase the reliability of CM Syndrome diagnosis and treatments. However, this kind of study design is removed from the process in real clinical practice in which practitioners formulate their own CM Syndrome diagnoses. The use of fixed lists also may not be applicable if there is a lack of data on CM Syndromes in the literature from which to compile a Syndrome list. For example, a study of reliability of CM diagnosis and treatment of irritable bowel syndrome (IBS)(Sung et al., 2004) did not find a satisfactory level of agreement amongst four practitioners in the diagnosis, treatment principle and the applied formulae, even though four common CM Syndromes of 'Chronic Diarrhoea' had been chosen for the diagnosis evaluation, and a follow-up

discussion was held amongst the practitioners after interviewing and examining the patients together. The concept of 'Chronic Diarrhoea' in ancient Chinese medical texts may not be the same as IBS.

6.5 Reliability of Chinese medicine diagnosis in osteoarthritis

The term 'osteoarthritis' (OA) did not exist in ancient Chinese medical books. As mentioned earlier, in CM it is generally believed that OA should be categorised as 'Bi syndrome', specifically 'Bi syndrome of bone'. As discussed previously, degenerative rheumatic diseases like OA or inflammatory rheumatic diseases such as rheumatoid arthritis can both also be described as Bi Syndrome. In other words, there is not a direct one-to-one correspondence between OA and Bi Syndrome.

The official clinical guideline of the People's Republic of China, *Criteria of Diagnosis and Therapeutic Effect of Disease and Syndromes in Traditional Chinese Medicine* (China State Administration of Traditional Chinese Medicine, 1994) has set up diagnosis criteria for OA which integrates CM principles with western medicine examinations including clinical symptoms, physical signs, X-ray examination and laboratory tests. There are three Syndromes of OA described in this guideline:

- 'Deficiency of Kidney Essence'
- 'Cold Blockage with Deficiency of Yang'
- 'Blood Stagnation'.

However, more Syndromes are described in the literature and used for guiding treatment, particularly combinations of Syndromes. These include:

- 'Syndrome of Damp and Heat Accumulation'
- 'Syndrome of Phlegm Blockage'
- 'Syndrome of Deficiency of Liver Blood'
- 'Wei Syndrome'.(Xiao, 2004, Qu and Xiao, 2008, Xiao and Zheng, 2003, Cao et al., 2006b, Min et al., 2003).

This is likely to be due to the different emphases and understanding of the pathogenesis of OA by different academics, researchers and practitioners in CM. These should be considered experience-based conclusions rather than evidence-based. There is no widely recognised OA outcome variables specifically related to CM assessments also.

6.6 Reliability of diagnosis in western medicine

Like in CM, there are variable levels of agreement in diagnostic methods used in western medicine which are also influenced by the doctor's experience. The accuracy and reliability of history-taking and conduct of a physical examination, two key components of clinical diagnosis in western medicine, have been of concern in medical education and clinical practice time for a long time.(Joshua et al., 2005, Ponnamperuma et al., 2009)

A literature review and analysis (Joshua et al., 2005) suggested there were considerable variations in the sensitivity, specificity and reproducibility of many time-related physical signs observed during the physical examination. Studies have shown some aspects of the physical examination to have low inter-rater reliability. For an example, two physicans were given a summary of a patient's history and the other two were without knowledge of the history. They then assessed respiratory signs of 202 unselected patients respectively within a period of two hours. The two groups of doctors showed poor inter-observer agreement for signs and diagnoses.(Gjłrup et al., 1984) This study also indicated that the patient's history did not contribute a higher Kappa value between the pair of doctors who had the history information. (Gjłrup et al., 1984) However, another study indicated that the reliability between two doctors in a neurologic examination could be increased if the second physician has been informed about the patient's history and other additional examination results.($\kappa > 0.6$) (Vogel, 1992)

The level of agreement amongst doctors for a range of physical signs is variable. An evaluation of the inter-rater variation among four doctors of neurological signs found out that the highest reproducibility was found for facial palsy and anisocoria, and the lowest for knee jerk, elbow extension force and finger-nose test.(Hansen et al., 1994)

This study also indicated that greater clinical experience might contribute to a reduction in variation amongst doctors. (Hansen et al., 1994)

Accuracy also plays an important role in medical diagnosis. Physical examinations can achieve more accurate results by standardising clinical performances or examining more frequently (Joshua et al., 2005, Vermeulen et al., 2007), even though this may not be practical for all diagnostic tests. For example, the diagnosis of hypertension can be verified by examining patients on more than one occasion. Use of laboratory tests can also contribute to a better diagnostic accuracy.(Manchikanti et al., 2009)

However, there are still some difficulties with increasing the reproducibility of the physical signs examination and history taking. A multi-centre study of stroke diagnosis (Shinar et al., 1985) showed inter-observer agreement was lower for history-taking than for neurologic examinations. There were only two history variables amongst 17 items in which raters reached moderate agreement alcohol intake within 24 hours of onset ($\kappa = 0.65$) and the last glucose intake ($\kappa = 0.46$). (Shinar et al., 1985) Although 27 physical examination variables amongst 47 items achieved 'moderate' to 'substantial' levels of agreement ($0.40 < \kappa \leq 0.80$), the Stroke Data Bank studies demonstrated that human observation and verbal communication is readily associated with inter-observer variations. They also found that the use of clear definitions of findings from history-taking and the physical examination could reduce unreliable diagnosis.(Gross et al., 1986, Shinar et al., 1985)

6.7 Conclusion

CM diagnosis is an integrated process. It starts with data collection using the four diagnostic methods then the data is analysed according to several theories including two major theories, the Eight Guiding Principles and Zang-Fu Theory. This is the process of Syndrome differentiation (data analysis). It concludes with the disease/disorder and Syndrome diagnosis. If the individual diagnostic observations (data) are unreliable, there can be less confidence that CM Syndrome diagnosis will be reliable, since this involves analysis and synthesis of individual diagnostic variables according to CM theories. If CM Syndrome diagnosis is not consistent, then treatment may be inconsistent.

The information about the reliability of CM diagnosis is still incomplete to date. Only one previous study assessed the reliability of three of the four diagnostic methods, and CM diagnosis according to the Eight Guiding Principles and Zang-Fu Theory. However, the reliablity of CM diagnosis has not been assessed as an entire system, that is, *all four* diagnostic methods, the Eight Guiding Principles and CM Syndrome differentiation in the one study. If the reliability of data collection cannot be guaranteed at the first step in diagnosis, then it is unlikely that there will be agreement on the CM Syndrome amongst the practitioners who have analysed the data via the process of Syndrome differentiation (i.e. Eight Guiding Principles, Zang-Fu Theory and other theories). There are fundamental questions- where is the problem in the consistency? Does it happen at the level of data analysis or the basic level of data collection?

Therefore, we conducted a reliability sub-study as part of a clinical trial into the efficacy of Chinese herbal medicine in the treatment for OA, assessing the reliability of the whole process of CM diagnosis as the first purpose of this sub-study. There is little objective knowledge of the Syndromes of OA standing on the empirical practice. Although OA has been traditionally treated as Bi Syndrome, this opinion has not been verified by testing its reliability. It is necessary to assess the reliability of CM diagnosis process and Syndrome diagnosis in OA to establish the CM characteristics of OA since treatment follows diagnosis. This was the second purpose of the reliability sub-study. Lastly, if CM diagnostic variables are reliable then they could be also used as OA outcome variables in the clinical trial of the efficacy of Chinese herbal medicine in treating symptoms of OA of the knee, in addition to other (western) endpoints like the WOMAC scale (Western Ontario and McMaster Universities Arthritis Index). This was the third purpose of this sub-study. The study results will be discussed in chapter 9.

Table 6.1 Inter-rater reliability studies of Chinese medicine Syndrome diagnosis

Study	Subjects	Observers	Study Design	Statistical test	Results
(Birch and Sherman, 1999)	16 CM acupuncture texts or articles	Literature study only	Examined the consistency of Syndrome diagnosis and acupoints choice described in selected literature regarding the treatment of low back pain	No information	1). 24 diagnostic Syndromes have been reported in total; 2). Only 4 Syndromes were described by at least 50% of the texts; 3). 4 acupoints (BL-23, BL-40, GV-3 and Ashi) were used regardless of Syndrome diagnosis 4). Substantial variation in recommended acupoints
(Hogeboom et al., 2001)	6 patients with chronic low back pain	6 licensed acupuncturists (median 9 years practice experience)	6 patients were assessed by 6 acupuncturists respectively;36 sessions were performed on the same day with 6 sessions occurring simultaneously; No discussion between raters Practitioners were asked to choose from 11 pre-selected Syndromes and allowed to add additional diagnoses, plus write down the nature of the	Kappa statistic for the inter-rater agreement test, no information of Kappa values; Prescribed acupoints were analysed by Jaccard coefficient and Kruskal-Wallis	1). 20 diagnosis and 65 acupoints were reported; 2). Poor agreement on 11 specific Syndromes 3) Using the Eight Guiding Principles for diagnosis was dependent more on the practitioner's preference regardless of who the patient was 4). Only one acupoint (BL-23) was reported for the majority sessions, and only 15-20% of acupoints were

			disharmony according to the Eight Principles and prescribe acupoints	test.	suggested for the same patient by at least half of the 6 practitioners.
(MacPherson et al., 2004)	148 patients with low back pain	6 acupuncturists with at least 3 years practice experience	A shortlist of Syndromes (Qi and Blood Stagnation, Bi Syndrome, Kidney Deficiency and Other) was used for Syndrome diagnosis; 6 practitioners treated at least 20 patients each (mean 24.7) and recorded applied acupoints. One of 6 acupuncturists re-examined some of other practitioners' patients independently for the diagnostic concordance test.	Inter-rater reliability was assessed in terms of percentage agreement and Kappa coefficient; Chi-square test was used for analysis of association between diagnosis and treatment	1). More than one Syndrome was diagnosed for 65% patients; 2). The agreement on Syndrome diagnosis re-examination ranged from 47% to 75% for primary Syndromes (0.00, no better than chance $\leq \kappa \leq$ 0.59, moderate agreement), and from 56% to 80% for secondary Syndrome (0.25, poor agreement $\leq \kappa \leq 0.67$, good agreement) 3) A highly significant association ($p <$ 0.005) between diagnosis and prescribed acupoints 4). The most frequently used point was BL-23 and the lowest two Huatuojiaji points.
(Sung et al., 2004)	39 patients with irritable bowel syndrome (IBS) in	4 licensed CM practitioners each with more	Phase I of study: All of patients were seen by four practitioners respectively and each	Percentage agreement and Kappa values	1). Phase I: Mean agreement rates in diagnosis, treatment principles and prescriptions were 57% ($\kappa = 0.11$),

	the phase I; 15 IBS patients recruited in phase II; 65 IBS patients and 17 controls patients recruited in phase III of the study	than 5 years of experience. Compared as 6 pairs for diagnosis agreement	practitioners was asked to choose the possible syndrome diagnosis from a pre-selected four diagnoses and record their corresponding treatment principles and herbal formulae. Phase II of study: 4 practitioners were asked to see the patients together in order to reach consensus. 15 patients were interviewed in total. Phase III of study: similar to phase I, Four practitioners were ask to diagnose IBS and non-IBS patients independently.	were used for statistic	58% ($\kappa = 0.16$) and 52% ($\kappa = 0.29$) respectively 2). Phase III: Mean agreement rates in diagnosis, treatment principles and prescriptions were 80% ($\kappa = 0.34$), 81% ($\kappa = 0.37$) and 80% ($\kappa = 0.34$) respectively 3). Comparing phase I and III: There were significant improvements in the mean Kappa values in syndrome diagnosis ($p = 0.015$) and treatment principles ($p = 0.002$), not in treatment regime.
(Zhang et al., 2004b)	39 patients with rheumatoid arthritis (RA)	3 TCM practitioners with at least 5 years experience	A questionnaire completed by patients was used as the Inquiry component of Four diagnostic methods. A pilot study on 19 RA patients was conducted to build up a syndromes list (10 Syndromes categories)	Percentage agreement between each of the 3 rating pairs; Kappa analysis was used to assess the level of agreement	1). The average agreement on Syndrome diagnosis amongst the 3 practitioners was 28.2% , ranging from 25.6% ($\kappa = 0.23$) to 33.3%($\kappa = 0.30$) 2). The level of partial agreement (less stringent agreement definition) of syndrome diagnosis amongst the 3 practitioners increased to 64.8% ,

			Each patient was interviewed by three practitioners respectively on the same day. Practitioners provided a Syndrome diagnosis and herbal prescription for each patient.	between any two practitioners	ranging from 48.7% (κ = 0.55) to 84.7%(κ = 0.87 3). The average agreement on herbal prescriptions amongst the 3 practitioners was 28.2% , ranging from 25.6% (κ = 0.27) to 33.3% (κ = 0.32) 4). The average agreement between the herbal prescriptions and the textbook recommendations was 93.2%, ranging from 87.2% to 100%
(Zhang et al., 2005a)	40 patients with RA	3 TCM practitioners with at least 5 years experience	Similar design to the previous study (Zhang G.G et.al 2004) in order to confirm the previous findings; adopted the previous syndromes list.	The same as the previous study (Zhang G.G. et.al 2004)	1). The average agreement on diagnosis amongst 3 practitioners was 31.7%, ranging from 27.5% to 35% 2). The average agreement between the herbal prescriptions and the textbook recommendations was 91.72%, ranging from 85% to 100% 3).No significant difference in Syndrome diagnosis and herbal prescriptions was found between this.study and the previous one (p > 0.05)

(Coeytaux et al., 2006)	37 patients with frequent headache	3 licensed acupuncturists with experience in TCM	Practitioners conducted clinical interviews and physical examinations for each patient separately. Practitioners were asked to choose from a pre-selected Syndromes list, including organs/meridians (9 choices), disharmony factors (7 choices) and dysfunction types (4 choices), in addition to prescribed acupoints (up to 8 points)	No information	1). 89% patients were diagnosed by at least one practitioner as having Qi disharmony. 2) 65% patients were diagnosed by at least two practitioners as having Qi disharmony 3) 53% patients were diagnosed by at least two practitioners as having Liver disharmony. 4) 27% patients were diagnosed by all three practitioners as having Liver disharmony 5) LR-3, LI-4 and GV-20 were the most common used points.
(Zhang et al., 2008a)	42 patients with RA	3 TCM practitioners with at least 5 years experience (the same doctors as the previous studies)	Similar design to the previous two studies (Zhang G.G et.al 2004, 2005), plus a prior training session on TCM diagnosis which featured a case study and open discussion.	The same as the previous study (Zhang G.G. et.al 2004, 2005)	1). Average agreement on Syndrome diagnosis between at least 2 practitioners ranged from 64.3% (κ = 0.49) to 85.7% (κ = 0.76) 2) Significant improvement in percentage of agreement on Syndrome diagnosis compared to previous two studies. ($p < 0.001$)

(O'Brien et al., 2009a)	45 patients with hypercholesterolemia	3 practitioners with formal CM education: 2 of them had over 20 years experience and the other had been in part-time practice for 5 years	CM assessment form was developed which included the Four Diagnostic Methods and Syndrome diagnosis based on the Eight Principles and Zang-fu theory. 3 practitioners assessed the patients on the same day. Practitioner 1 completed Part A (case history) and B (CM examinations) of the form, while practitioner 2 and 3 completed Part B separately and read Part A only. No discussion amongst 3 practitioners Open-end CM Syndrome diagnosis	Kappa analysis was used to assess the level of agreement between three practitioners	1). Level of agreement on the Eight Guiding Principles amongst three practitioners ranged from 24% (κ = 0.15, slight) to 88% (κ = 0.87, almost perfect) 2). Level of agreement on the Eight Guiding Principles between at least two practitioners ranged from 88% (κ = 0.46, moderate) to 100% (κ = 1.0, almost perfect) 3). Most reliable Syndrome variable of the Eight Guiding Principles was the location of disorder “Interior/Exterior”. 4). Highest level of agreement for Syndrome diagnosis according to Zang-fu theory amongst all three practitioners was 24% (Spleen Qi Deficiency), and other diagnoses were extremely poor. 5). 15 different single syndrome diagnoses reported.

Chapter 7 Methods

7.1 Introduction

This chapter describes the relevant diagnostic assessment techniques and methods that were used in the two empirical studies: a pilot study into the efficacy of a Chinese herbal medicine in the treatment of symptoms of osteoarthritis (OA) of the knee and a study of the reproducibility of Chinese medicine (CM) diagnosis in Australians with OA. The western medical assessment and related monitoring indices include anthropometric measurements, haemodynamic measurements, blood tests, radiological examination, functional measurement of OA symptoms, diet diary and habitual physical activity measurement. A CM diagnosis assessment tool was used for the purposes of recording the results of a CM examination and investigation of the reliability of CM diagnosis.

A summary table of the clinical study design is set out in the Table 7.1.

Table 7.1 Summary of the study design

Design	Description
Trial name	Evaluation of the efficacy of a Chinese herbal medicine in the treatment of patients with osteoarthritis of the knee
Design type	Randomised, double blind, and placebo controlled
Participants	Key eligibility criteria were based on the American College of Rheumatology (ACR) 1995 (Hochberg et al., 1995) and the ranking score of the Kellgren-Lawrence radiographic system (Kellgren and Lawrence, 1957)
Interventions	A CHM formua composed of six herbs was used as the active medicine; Lactose was used as the placebo
Objectives	To investigate the efficacy and safety of the CHM formula developed on the basis of an emerging CM theory in the treatment

	of symptoms of knee OA;
	To investigate the reliability of CM diagnosis in OA patients
Outcomes	The WOMAC Index was the primary outcome variable
	Level of agreement between two practitioners (reliability study)
Study site	The Centre for Clinical Trial (Nucleus Network, Melbourne) in cooperation with the Alfred Hospital (Melbourne)
Randomisation	Participants were all assigned to the treatment or placebo group in accordance with a computer-generated randomisation code in a sequential manner.
Dose and duration of treatment	Each subject attended a total of six clinic visits during the 12 weeks treating and 4 weeks follow-up period.
	The dose of the study medication/placebo was five capsules three times a day.
Recruitment	Participants were recruited through newspaper advertisements.
Satefy monitoring	Laboratory tests (serum chemistry, haematology, and urinalysis), 12-lead electrocardiogram, concomitant medication review and adverse event reports
Ethics approval	Ethics approval received from theAlfred Hospital Human Research Ethics Committee (HREC) (Alfred Health Project 98-08, approved on 20 Apr 2009) and Victoria University HREC
Statistics analysis	Normality of the data was assessed using the Shapiro–Wilk W test
	The Paired Student T test was used for within-group analyses
	The Independent Sample T Test was used for between-groups analyses

The Cohen's Kappa coefficient was applied in the the reliability study

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7.2 Anthropometric measurements

7.2.1 Age and gender

Age and gender of participants was recorded. Age was calculated based on the patient's birth date as recorded on his/her photo identification. The mean age and its standard deviation of the study population for each group were calculated via the following formula:

$$\sigma = \sqrt{ \Sigma(X - M)^2 \div (n - 1) }$$

σ is the standard deviation (accurate to two places of decimals)

X is value of an individual age

M is the mean value (age)

n is size of the sample (number of subjects in the study)

The proportion of females and males in each group was also recorded.

7.2.2 Weight, height and body mass index

Weight was measured by a light industrial scale (manufactured by Avery Berkel, Model No. HL122 [Serial No. EQ300766]). Its operation temperature ranges from -10 Celsius to 40 Celsius and capacity is 300kg within the resolution of 0.05 kg. Participants were asked to remove shoes, socks and bulky clothing prior to weight measurement. The weight reading was rounded to 0.1 kg. Height was measured by a standard tape measure to the nearest 1 cm with shoes removed.

BMI was calculated according to the formula of weight in kilograms divided by the square of height in metres (kg/m^2).

The above measurements were conducted at the each visit except for height which was measured at the screening visit only.

7.3 Haemodynamic measurements

Haemodynamic measurements were taken at each visit for every participant during the trial. Patients were asked to rest for five minutes before measurements. A vital signs monitor was used to measure blood pressure, heart rate and body temperature (Physiologic Monitoring System 300 series, manufactured by Welch Allyn [Serial No. JA003135]). The monitor consists of an inflatable cuff, a thermometer probe and a measuring and reading unit.

Peripheral systolic and diastolic blood pressures were recorded in millimetres of mercury (mmHg) and heart rate was recorded in beats per minute (BPM). Blood pressure was measured on the inside of the elbow at the brachial artery with the cuff placed smoothly and snugly around an upper arm, at roughly the same vertical height as the heart while the subject was seated with the arm supported. No clothing was between the blood pressure cuff and the arm. The same method was conducted if the patient was lying down. Blood pressure and heart rate were taken in the same measurement session and the patient's same arm was used for the measurement at each visit and noted in the source documents.

Body temperature was detected by insertion of a thermometer probe into the mouth (the tip of the thermometer was covered by a single use plastic cover). Readings of this fast-reacting digital thermometer were accurate to 0.1 Celsius.

7.4 Blood tests

Blood sample collection was conducted in the clinical trial base of the Centre for Clinical Studies, Nucleus Network (located in Prahran, Victoria, Australia) by registered nurses. The participants were required to fast for at least 8 hours before taking blood. Blood samples were taken at the screening visit, end of Week 2, Week 6 and the end of Week 12 (post-randomisation).

Blood analysis was conducted in the Pathology Department of the Alfred Hospital (in Prahran, Victoria, Australia). Blood tests, as part of safety monitoring, included: full

blood count, liver function tests (alanine transaminase, aspartate transaminase, total bilirubin), renal function tests (blood urea nitrogen, creatinine, blood uric acid), fasting blood glucose, electrolytes, lipid profile (serum total cholesterol, serum triglyceride, high-density lipoproteins), clotting tests (prothrombin time, activated partial thromboplastin time), erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (high-sensitivity CRP) and rheumatoid factor (RF). ESR, CRP and RF are also effective biomedical markers used in the differential diagnosis of rheumatoid arthritis from OA. (Walker et al., 1997, Ward, 2004)

7.5 Radiography examination

Radiography of knee in the antero-posterior view was performed in the Radiology Department of the Alfred Hospital at the screening visit, if this had not been performed during the previous three months. In most of cases, X-rays of both of knees were taken, except for some patients who only had a diagnosis of OA in only one knee or had a prosthetic (other) knee. The results of knee X-rays were interpreted by the same radiologist throughout the clinical trial.

Radiographic evidence of osteophytes is an essential criteria for diagnosis of OA of the knee in the American College of Rheumatology classification criteria.(Hochberg et al., 1995) and formed part of the inclusion criteria for this study. Radiographic evidence of OA was determined based on the widely accepted and validated Kellgren-Lawrence Grading Scale System for the tibiofemoral joint,(Kellgren and Lawrence, 1957, Kijowski et al., 2006) Participants with grade 2 or grade 3 severity of primary tibiofemoral OA were considered eligible for inclusion in the study, including patients with only one knee that satisfied the criteria. Grade 0, Grade 1 and Grade 4 were excluded: Grade 0 or 1 are considered normal and Grade 4 considered severe. The Kellgren-Lawrence Radiographic Grading Scale of OA of the knee is set out in Table 7.2.

Due to the fact that radiographic change is not particularly suitable for use as an OA clinical outcome variable in the assessment of slow-acting or disease modifying agents like herbal medicine,(Dieppe et al., 1997) radiography examination was conducted at the screening visit as part of assessing suitability for participation in the study only.

Table 7.2 Kellgren-Lawrence radiographic grading scale of ssteoarthritis of the knee

Grade of Osteoarthritis	Description
0	No radiographic finding of bony change or joint space narrowing
1	Doubtful joint space narrowing and minute osteophytic lipping
2	Definite osteophytes with minimal joint space narrowing
3	Multiple definite osteophytes, moderate joint space narrowing with some sclerosis and possible deformity of bone contour
4	Large osteophytes with severe joint space narrowing, severe subchondral sclerosis and definite deformity of bone contour

7.6 Functional measurements of osteoarthritis symptoms

7.6.1 WOMAC osteoarthritis index visual analogue scale (VAS)

7.6.1.1 Introduction

In the past, evaluation of the efficacy of treatment of knee OA of the knee has focussed on physical findings, such as range of movement, joint laxity or radiological findings. However the current research trend is to focus on analysis of the patient's personal experience of the therapeutic modality, since the purpose of treatment is relief of symptoms. Many questionnaires or rating scales have been developed for the evaluation of OA of the knee. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is the most extensively used, standardised instrument since it was published in 1986.(Bellamy and Buchanan, 1986)

The WOMAC Index is a valid, reliable and sensitive disease-specific, self-administered, health status measure for patients with OA of the knee and/or hip. It assesses clinically-important symptoms in three subscales of pain, joint stiffness and physical function. It

consists of 24 questions (5 related to pain, 2 related to stiffness and 17 related to physical function). These 24 questions in the WOMAC Index could be categorised into different joint motions associated with four daily activities: lying/sitting, standing/walking, bending and ascending/descending.(Angst et al., 2005) There are three versions or formats of the WOMAC Index available for clinical trials: a Likert Scale, Visual Analogue Scale (VAS) and a Numerical Rating Scale. The VAS is the most commonly used.(Bellamy, 2002, Theiler et al., 2002)

7.6.1.2 Validity, reliability and responsiveness of the WOMAC Index

Reliability, validity and responsiveness of the WOMAC Index has been demonstrated not only in studies investigating traditional non-steroidal anti-inflammatory drugs (NSAIDs) and arthroplasty interventions, but also in other complementary and alternative medicine modalities, such as physical exercise, massage, acupuncture and herbal medicine.(Song et al., 2003, Perlman et al., 2006, White et al., 2006, Winther et al., 2005) With respect to the sensitivity of the instrument, it has been found that the perceptible change in the disease status from the perspectives of the patient and physician could be observed with as little as 8-12 mm improvements on the WOMAC VAS.(Ehrich et al., 2000) With respect to validity, studies have demonstrated a moderate or strong correlation between the WOMAC and the Lequesne OA Index (another well-known OA instrument) and the Short Form-36 (SF-36) quality of life instrument, reflected by validity data from pain and physical function subscales.(Stucki et al., 1998, Wright and Young, 1997) In addition, the WOMAC Index was found more responsive than the Lequesne Index in patients with OA of the hip or knee, especially in the pain and function sections.(Theiler et al., 1999, Gentelle-Bonnassies et al., 2000) Likewise, data from a comparison study demonstrated the WOMAC to be more reliable in detecting functional improvement for rehabilitation interventions than the SF-36, including during a follow-up period.(Angst et al., 2001) However, another study of the administration of the WOMAC Index in OA patients waiting for total hip or knee joint arthoplasty suggested that it may not be appropriate to summate the scores of the five related dimensions of osteoarthritis pain, such as walking, stair climbing, sleeping, sitting and standing.(Stratford et al., 2007) In general, although there has been variable reliability reported for other commonly used pain measurement

scales, the WOMAC Index demonstrates internal consistency and test-retest reliability and that items of each subscale are related to each other(McConnell et al., 2001)

The WOMAC Index has also been translated into many different languages for multiple applications and the reliability and validity verified in diverse language forms such as Spanish, Italian, Turkish, Thai and Arabic language.(Tuzun et al., 2005, Villanueva et al., 2004, Salaffi et al., 2003, Guermazi et al., 2004, Kuptniratsaikul and Rattanachaiyanont, 2007, Wigler et al., 1999)

The WOMAC VAS version has been found to be slightly more sensitive than the Likert version in some studies, especially on the pain and stiffness subscales.(Bellamy, 2005) Therefore, the VAS version was chosen for use in this study.

7.6.1.3 Administration protocol for the WOMAC VAS

The WOMAC VAS consists of a horizontal line 100 mm in length with response options ranging from 'no' at one end (left hand side) to 'extreme' at the other. The patient is asked to mark on the line the point that represents his/her perception of his/her current state, anchored by the word description at each end.(Bellamy, 2005) The VAS score is calculated by measuring the distance in millimetres from the left hand end of the line to the point at which the patient intersects a mark on the line. (See Appendix 3)

The VAS score was calculated for each of the three domains (pain, stiffness and physical function), and a WOMAC global score was computed as the unweighted mean of all 24 items. Measurements were completed at the assessment visits (baseline, the end of Week 12 and the follow-up visit).

The method of data analysis adopted in this study was that described in the User Guide of the WOMAC statement,(Bellamy, 2005): if the patient placed his/her mark outside the end of the line, 0 was recorded when the placement is outside of the left end, and 100 if it was marked outside the right end. The use of an '×' was recommended instead of a tick ('√'). However, in the case where a tick was drawn, the point of inflection of the tick '√' on the line was used in calculating the distance from the end of the line. If the patient did not make a discreet intersection of the line, the data analyst dropped a line perpendicular

to the horizontal (VAS) line from the intersection of the '×' or the inflection part of the '√'.(Bellamy, 2005)

If the patient did not fill in the whole form of 24 questions, the following procedure was conducted.(Bellamy, 2005) The form was judged as invalid and was not used in the final analysis if more than two questions in the pain subscale, or two questions in stiffness subscale, or more than four items in physical function subscale were omitted. In the case where only one item in the pain subscale, one item in the stiffness subscale or 1 - 3 questions in physical function subscale were omitted, the average value (of that subscale) was used to replace the missing data using in the analysis.

7.6.2 Physician Global Assessment

The Physician Global Assessment is recommended as an outcome measurement in clinical trials of OA that assess efficacy of symptom-modifying drugs, especially in research related to pain.(Collins et al., 2001) It is available in the form of a VAS or a Likert scale.(Altman et al., 1996) Because there is no generally accepted method for measurement of this variable, the Likert scale was applied in this study, adopted from the study of Ehrich and colleagues.(Ehrich et al., 2000) The evaluation was conducted by the registered rheumatologist at both assessment visits (the baseline and the end of Week 12).

This assessment is comprised of two parts. In the first part, the Investigator Global Assessment of the Disease Status, the assessor (rheumatologist) is asked to do the following: Considering all the ways OA affects your patient, how would you rate him/her condition today by marking a '×' in one box below?'; 0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor.

In the second part (which is derived from the first part), at the end of study, the assessor is asked: 'Considering all the ways OA affects your patient, how would you rate him/her condition now compared with the beginning of the study with the therapeutic effect of the study medication?'; 0 = no response, absence of drug effect, 1 = poor, minor response, unacceptable, 2 = fair, definite response but could be better, 3 = good, good response, but less than the best possible anticipated response, 4 = excellent, the best possible anticipated response considering the severity and stage of the disease. (See Appendix 4)

7.6.3 Patient Global Assessment

The Patient Global Assessment has also been applied in some studies as an internal validation evaluation tool assisting the WOMAC index, to assess the patient's perception of the clinical severity of their OA condition.(Angst et al., 2005, Gentelle-Bonnassies et al., 2000) A standard question is asked: 'Considering all the ways your osteoarthritis affects you, how would you rate your condition today?'(Altman et al., 1996)

A VAS or Likert scale can be adopted in the Patient Global Assessment (recommended by a task force of the Osteoarthritis Research Society).(Altman et al., 1996) In this study, a 100 mm visual analogue scale was used, and the evaluation was conducted at assessment visits (the baseline, the end of Week 12 and the follow-up visit). The patient was asked to anchor an '×' mark on the horizontal line, with the instructions that the values 'very poor' corresponded to the left hand end and 'very good' corresponded to the right hand end of the line. The procedure used for the VAS analysis for the Patient Global Assessment was the same as outlined for the WOMAC VAS assessment. (See Appendix 5)

7.6.4 Quality of life questionnaire

7.6.4.1 Introduction

The SF-36 Health Survey is a self-reported outcome questionnaire designed to assess health- related quality of life. It is the most widely used short instrument in studies of arthritis. The SF-36 contains 36 questions focussing on generic health status measures including physical functioning, social functioning, role functioning, psychological distress, general health perceptions, bodily pain, and psychological well-being.(Keller et al., 1999a) The instrument yields two health and wellbeing summary measures, one of physical health and one of mental health. It takes 6-9 minutes to complete. (See Appendix 6)

As a generic measurement it may, however have less power to detect change in functioning and well-being related to the specific condition of OA.(Keller et al., 1999a) Therefore, the strategy of this study was to include both a generic measure (SF-36) and

more specific indices (such as the WOMAC Index, Physician Global Assessment, Patient Global Assessment) to monitor the health outcomes of patients with OA. The SF-36 form featured Likert scales for its response options.

7.6.4.2 Validity, reliability and responsiveness of SF-36

There are many methods of analysing and interpreting the results from profiles of scores yielded through generic measures like the SF-36. A developmental and cross-validation study demonstrated that the generic SF-36 health profile was useful in comparing arthritis with other diseases and treatments and could be scored specifically in studies of OA and rheumatoid arthritis (RA), without substantial loss of information.(Ware et al., 1999) Other cross sectional assessments found the SF-36 was a valid instrument for the assessment of the health burden of arthritis, it correlated with the physician and patient global assessments, and was suitable for clinical trials of alternative medicine treatments.(Kosinski et al., 1999b, Tuttleman et al., 1997) The construction and scoring of the SF-36 scales has determined the reliability of psychometric assumptions amongst clinical trials with arthritis. An analysis conducted on four trials tested the completeness of the item-level and scale-level data of SF-36 and item-internal consistency, and confirmed that the SF-36 was a psychometrically sound tool to assess the general health status of participants with arthritis. There was little variation in data completeness, psychometric criteria, and the scale score distribution.(Kosinski et al., 1999a)

Two studies (Keller et al., 1999b, Kosinski et al., 2000) have suggested that the SF-36 arthritis-specific index may be more effective to assess changes in variables in OA trials. However the general SF-36 Health survey was still used as a measurement tool in this study as this assertion has not been substantiated or confirmed in other studies.

7.6.4.3 Administration protocol for the SF-36

The SF36 was self-administered at three assessment visits: at the randomisation visit (week 1), the post randomisation visit (Week 12) and the follow-up visit Patients were instructed to tick one box of each multiple choice question only. The investigator (myself, the Ph.D student) checked and clarified the answers immediately on completion by the study participants, in cases where there were dual ticking or omissions.

7.6.5. Habitual physical activity measurement

Assessment of possible change in physical activity, a potential confounding variable, was assessed in this study. Amongst many questionnaires, the Baecke Questionnaire is one of the most widely used tools for assessing physical activity in older adults with chronic conditions (Baecke et al., 1982) It has been found to be reliable and valid in several studies where it was used to measure habitual physical activity at work and during leisure time.(Ono et al., 2007, Pols et al., 1995, Pols et al., 1996)

The Baecke Questionnaire of Habitual Physical Activity was administered at three time points: at baseline, the end of Week 12 and the follow-up visit. The questionnaire is self-explanatory and required participants to answer questions that were scored on a Likert scale. The patients were asked to tick one choice only for each question. See Appendix 7.

7.6.6. Chinese medicine assessment

7.6.6.1 The Chinese medicine assessment form

CM diagnosis is based on systematic collection and interpretation of a range of signs and symptoms according to several CM theories. As previously explained (Chapter 2), 'Syndrome Differentiation' forms a key part of diagnosis. A CM assessment form was used to systematically record CM diagnostic information and investigate the reliability of CM diagnosis in OA patients.

A CM assessment form was originally created and developed by a group of Australian researchers in consultation with seven CM practitioners and academics from Australia and Europe in 2003 and applied in a study of the reliability of CM diagnosis in hypercholesterolaemic Australians.(O'Brien et al., 2009b) The four domains of diagnostic methods used in CM covered in the CM assessment form are: Inquiry (case history), Inspection, Auscultation/Olfaction and Palpation as set out in the State Administration of Traditional Chinese Medicine's *Advanced Textbook on Traditional Chinese Medicine and Pharmacology*,(State Administration of Traditional Chinese Medicine, 1995) a standard textbook used in CM curricula in China at the time. This assessment form has been

modified to include specific questions relating to the knee joint. These new questions were developed in consultation with a senior rheumatologist.

The assessment form was divided into two parts. Part A was a case history form consisting of a series of questions relating to bodily functioning, with extra questions about the knee joint added for this study. For most questions, information was recorded as categorical variables and practitioners were required to choose one from a limited range of answers. Part B was designed to record information relating to visual inspection (including tongue diagnosis), auscultation/olfaction and palpation (including pulse diagnosis). The categorical format was applied in this part also.

The final section of the CM assessment form contained a Diagnosis Summary Page. Practitioners were asked to make a diagnosis in terms of the Eight Guiding Principles which is the foundation of Syndrome identification in CM (see Chapter 2), and to indicate one or more CM Syndrome diagnoses according to Zang-Fu Theory (see Chapter 2). Practitioners were also required to indicate which Zang and Fu organs were involved, which signs/symptoms lead them to their diagnosis and to rank these in order of importance.

The CM assessment form is included in Appendix 8.

7.6.6.2 Validity of the Chinese medicine assessment form

Validity is the degree to which variability (individual differences) in participants' scores on a particular measure reflects individual differences in the characteristic or constructs we want to measure.(Merriam, 2009) There are three main types of measurement validity: face validity, construct validity and criterion validity.(Jakobsson, 2009)

Face validity refers to the extent to which a measure 'appears' to measure what it is supposed to measure, and relates to whether a test appears to be a good measure or not. The CM assessment form was developed on the basis of the Four Diagnostic Methods, which are the basic diagnostic methods in traditional CM taught in medical university curricula in China, as set out in the textbook endorsed by Chinese government's authority on Chinese medicine, the State Administration of Traditional Chinese Medicine

(SATCM). The sections of CM assessment form relating to Inquiry, Inspection, Auscultation/Olfaction and Palpation allow the systematic recording of comprehensive observational data and CM Syndrome diagnoses. In the Inquiry section of the assessment form, the 'ten rhythmic questions' of case history taking, as set out in the SATCM textbook, are covered. It is therefore argued that the CM assessment form has face validity.

Construct validity is assessed by studying the relationships between the measure of a construct and scores on measures of other constructs, and assessing whether it can cover the full range of combinations of the behaviour domain to be measured.(Merriam, 2009, Test et al., 2005) The original CM assessment form comprehensively covers all four diagnostic methods, developed on the basis of a standard textbook and by consensus between seven CM practitioners and academics. Furthermore, the CM assessment form included a special section related to the knee joint, which was the focus of the study. It can therefore be argued that the assessment form has content validity in the study of knee OA in the treatment of Chinese herbal medicine.

Criterion validity compares the results of a measure with a 'gold standard' or criterion that is known or believed to be close to the truth, and refers to the extent to which a measure distinguishes participants on the basis of a particular behavioural criterion and also reflects the success of measures used for prediction or estimation.(Merriam, 2009) There are no commonly used CM assessment forms that are readily available, though there was a pilot study (Wang, 2004) to develop and validate a traditional Chinese medicine (TCM) questionnaire in patients with OA of the hip or knee. In that study, the TCM assessment form only addressed certain components of TCM diagnosis, simplifying the Four Diagnostic Methods to questions about pain, stiffness and more general questions about other symptoms related mainly to OA and underlying Bi Syndrome. The questionnaire used a Likert scale, (with opinion such as none, mild, moderate, severe and extreme) for the responses. Insufficient data is able to be collected using this questionnaire that would allow a fuller clinical picture upon which a more definitive diagnosis could be made, and therefore it is of limited use.

The CM assessment form originally developed by O'Brien and colleagues,(O'Brien, 2006) and further developed in this study is much more comprehensive. In this study, the form not only covered by the essential points of the Four Diagnostic Methods in detail, but it also included a special section relating to the signs and symptoms of OA of the knee. In normal clinical practice, practitioners may vary in the questions they ask during a consultation and what they record. However, the description of the Four Diagnostic Methods set out in the SATCM's standard textbook, upon which the CM Assessment Form is based, is regarded as (systematised) standard clinical information to be collected in an examination. The clinical information in this Assessment Form simulated everyday clinical practice by recording clinical data in a manner that allows the data to be readily analysed statistically. Therefore, it is argued that the CM assessment form used in this study has the criterion validity in term of the theoretical structure and the real practice of CM diagnosis.

7.6.6.3 Protocol

The CM assessments were conducted by two CM practitioners including the author of this thesis at the baseline visit. The two practitioners were not allowed to discuss the cases before and after diagnosis in order to minimise the potential to influence each other.

In Part A of the assessment form (case history), a standard form of words was used, with the option to ask additional questions and record more information if necessary. Following completion of the case history, the Inspection, Auscultation and Palpation components were conducted and Part B of the assessment form completed, including the diagnosis summary page. The patients were prohibited to take food and any medications 30 minutes before the CM assessments since these could alter the colour of the tongue coating, and the thickness and moisture of the tongue coating could change after eating or scraping the tongue.

Chapter 8 The Study Herbal Formula

8.1 Introduction

The formula used in this clinical study is based on one created by the Shanghai Shuguang Hospital, P.R. China: the Yang Xue Ruan Jian formula. The name translates in English as 'benefiting (nourishing) blood and relaxing stiffness formula'. This formula is composed of Bai Shao (*Radix Paeoniae Lactiflorae*), Qin Jiao (*Radix Gentianae Macrophyllae*), Mu Li (*Concha Ostreae*) and Zhi Gan Cao (*Radix Glycyrrhizae Preparata*), to which the herbs Dang Gui (*Radix Angelicae Sinensis*) and Huai Niu Xi (*Radix Achyranthes bidentata*) were added to create a new formula, the Bai Niu capsule.

This chapter will describe the structure and function of the Bai Niu capsule in terms of CM theory, the actions and contraindications of the individual herbs from the CM perspective, and evidence of the efficacy and safety of the formula. It will also describe how the Bai Niu Capsule has been produced for the study.

8.2 The theoretical basis of the Bai Niu capsule

This new formula has been developed in accordance with the emerging theory described previously in Chapter 5 that suggests that OA should be treated as a combination of Wei Syndrome (predominantly) and Bi Syndrome, with a therapeutic emphasis on nourishing the Liver and soothing the tendons and secondarily tonifying the Kidney and to a lesser extent, eliminating exogenous pathogenic Wind-Dampness.

As described previously, Chinese herbs are usually combined in a medicinal formula of typically 3-12 herbs. Every medicinal substance has specific actions and each ingredient in the formula should be carefully balanced in quality and quantity to strengthen the efficacy of the formula while reducing potential side effects. The herbs are not simply added randomly but combined according to particular principles, discussed previously (see Chapter 2).

The treatment principles of the Bai Niu capsule are nourishing the Liver (Blood), soothing the sinews, and to a lesser extent, tonifying the Kidney and eliminating exogenous factors,(Cao et al., 2006b) In the Bai Niu capsule formula, Bai Shao can be

regarded as the ‘monarch’ or ‘chief herb’ with its functions of nourishing Liver Blood and soothing sinews and stopping pain.(Bensky et al., 2004) To reinforce the function of nourishing the Liver Blood, another principal herb, Dang Gui, has been added. Dang Gui also has the function of improving Blood circulation.(Bensky et al., 2004) Qin Jiao and Huai Niu Xi can be considered as the ‘minister herbs’ in this formula (Qin Jiao was also considered a minister herb in the Yang Xue Ruan Jian formula), as they support the monarch herb to achieve its major actions on the body, and also treat the accompanying symptoms and address co-existing disharmonies. Qin Jiao can regulate Blood circulation and soothe the sinews, expel external Wind and Dampness and stop pain.(Bensky et al., 2004) Huai Niu Xi can tonify the Kidney and Liver, strengthen bones and tendons, and also promote Blood circulation and guide other herbs downwards to the lower limbs (Bensky et al., 2004).

Mu Li’s astringent quality can help prevent the loss of Yin and Blood, along with its ability to soften nodules and hardness.(Bensky et al., 2004) It was used in the formula as an ‘assistant herb’ to reinforce the effects of the monarch and minister herbs. In addition, according to CM theory Mu Li targets the Kidney and Liver meridians, so it can function to guide the action of the formula to these meridians. Zhi Gan Cao acts as a guide herb, harmonising and integrating the effects of other herbs. As a herb that can tonify Qi, it can also help nourish Blood (Qi being part of Blood).

8.3 Evidence of the efficacy and safety of the formula

Although this study was a pilot clinical trial of the Bai Niu capsule, there have been previous studies conducted that have verified the efficacy and safety of the Yang Xue Ruan Jian formula. Those findings could be regarded as a preliminary research of Bai Niu capsule which is derived from the Yang Xue Ruan Jian formula. There were two clinical trials (Cao et al., 2004b, Shi et al., 1994) which have been conducted in the past ten years since the Yang Xue Ruan Jian formula was introduced in the Shuguang Hospital, though only one of them was a randomised and double-blinded study. Three animal studies were conducted to investigate its anti-inflammatory and analgesic effects.

8.3.1 Animal studies of Yang Xue Ruan Jian formula

Studies have been conducted to assess the anti-inflammatory and analgesic effects of the herbal formula upon which the Bai Niu Capsule has been based, the Yang Xue Ruan Jian formula, using animal models.(Cao et al., 2004a) In an experiment using xylene-induced auricle oedema in Kunming mice, the swelling rate in the treatment group treated with intra-gastric application of the formula in three dosages (low, medium and high) was significantly lower than in a placebo (saline) group ($p<0.05$). In addition, there were no statistical difference between the treatment groups and an Ibuprofen control group.(Cao et al., 2004a).In a carrageenan-induced paw inflammation test conducted in Sprague-Dawley rats, the oedema rates of the treatment group were significantly lower than in the placebo (saline) group particularly at 2 hours and 4 hours after injection of carrageenan ($p<0.05$), whilst there was no significant difference between the Ibuprofen control group and the placebo group during that period.(Cao et al., 2004a) The analgesic effect of Yang Xue Ruan Jian formula was evaluated by 'hot-plate' and 'acetic acid' analgesic test methods in mice, and indicated that the herbal medicine could increase the pain threshold particularly at the one hour stage, but that the effect was lower than Ibuprofen.(Cao et al., 2004a)

There are also two published articles of animal experiments investigating the effects of the Yang Xue Ruan Jian formula on histopathology and histomorphology using Swiss mice and models of knee OA.(Shen et al., 1995, Wang et al., 1998) In one experiment (Shen et al., 1995) the researchers created the knee OA model through operating on the knee medial accessory ligament and anteromedial aponeurosis and forcing the mice to walk 30 metres everyday in an experiment box since the second day post-operation. Intragastric administration was applied to a treatment group (Yang Xue Ruan Jian formula), a control TCM group (a Kidney Tonifying formula), a Fenbid group, and a placebo model group as well as a normal mice group (non-operation group). Each group was stratified into three different groups in which the medical treatment was only started after the second day post- operation (two weeks treatment in this group), or the second week post-operation (four weeks treatment in this group), or the fourth week (four weeks treatments in this group). This design was intended to reproduce the different stages of OA in order to investigate the effectiveness of the medicine for mild and moderate and severe OA. The second study (Wang et al., 1998) had a similar study procedure and

created the model by operating on the heel tendon and forcing the mice to walk 48 metres per day, five days a week during the post-operation period. Two sub-groups were designed within each group: one received the one months treatment beginning in the fourth month post-operation and the other received one month's treatment beginning in the the sixth month post-operation. In this study, a control TCM group was added (treated with an 'Invigorating Spleen' formula that focussed on tonifying the Spleen). Indices including thickness of articular cartilage, density of bone trabecula of subcartilaginous osseous lamella, density of chondrocyte, and deterioration of chondrocyte as well pathological change in the synovial membrane were used as assessment criteria in both experiments.

Results of these two animal experiments indicated that the Yang Xue Ruan Jian formula could reduce deterioration of chondrocytes and decrease inflammation and hyperplasia of the synovial membrane compared with the other control groups ($p < 0.05$) with one exception: there was no difference between the Kidney Tonifying formula control group and the Yang Xue Ruan Jian formula group in reduction deterioration of chondrocytes. It was also found that Fenbid could decrease inflammation of the synovial membrane in the early stage of OA, but could not influence deterioration of chondrocytes ($p > 0.05$), which is the main pathological change in intermediate and advanced stages of OA.

8.3.2 Clinical studies of Yang Xue Ruan Jian formula

The original form of Yang Xue Ruan Jian formula was as a liquid decoction. The first clinical study of this formula,(Shi et al., 1994) conducted in patients with OA of the knee showed significant improvement according to the severity indices in the group treated with the decoction compared with another Chinese herbal medicine control group and the western medicine control group (Fenbid), particularly in reducing knee pain. However, there was lack of information about randomisation and blinding, as well as adverse events and statistical methods, so care needs to be taken in interpreting the result of this study.

A double-blind, randomised controlled clinical trial of the Yang Xue Ruan Jian formula in capsule form found a significant improvement in WOMAC scores in Week 2 and Week 4 (the end of treatment period) compared to the baseline data.(Cao et al., 2004b)

However, there was no significant difference in efficacy between the treatment group and Chinese patent medicine control group or the glucosamine group ($p>0.05$). Therefore, the study indicated the Yang Xue Ruan Jian formula had a similar efficacy to glucosamine which is used widely as a treatment in clinical practice. With respect to safety, this study (Cao et al., 2004b) reported a single case of urticaria amongst 30 participants in the treatment group which may have been related to the herbal medication, two cases of constipation and gum pain, and one patient who reported a bitter taste in the mouth after the trial, however these may not have been related to study medicine. No abnormal laboratory test results were found in participants of the trial.(Cao et al., 2004b)

8.4. Scientific studies of the herbal ingredients

8.4.1 Dang Gui

Dang Gui (also known as Dong Quai) is the root of *Angelica sinensis (Oliv.) Diels*, a fragrant perennial herb. It has commonly been used as a traditional Chinese medicine for thousands of years. According to CM theory, it can nourish and invigorate Blood, regulate menstrual disorders, eliminate pain and cramps, and lubricate the bowel, and is related to the Liver, Heart and Spleen meridians. In Europe and America, the root of Angelica has been used as a dietary supplement for woman's health also.(Zhao et al., 2003)

The pharmacologically active constituents of Dang Gui are ferulic acid, ligustilide, many kinds of volatile oils (such as butylidenephthalide and butylphthalide), polysaccharide, various coumarin derivatives, and significant amounts of vitamin A, B_{12}, C, and E.(Thorne Research Inc., 2004, Zhao et al., 2003) It has anticoagulant, haematopoietic, anti-tumour, and estrogen-like activity.(Yang et al., 2002, Wang et al., 2006, Ye et al., 2003, Yang et al., 2007b, Yang et al., 2006b) Dang Gui has been investigated widely for its clinical utilisation in cardiovascular diseases, menstrual irregularities, anaemia and tumours.(Thorne Research Inc., 2004) Dang Gui is frequently used in CM prescriptions for bone or tendon injuries and arthritis. For instance, a survey indicated that Dang Gui was the second most frequently used ingredient in 76 different oral patent Chinese herbal medicines for the treatment of OA, rheumatoid arthritis and degenerative arthritis. (Liu et

al., 2005a) Dang Gui was also the third most commonly prescribed herb in 703 oral herbal decoction formulae for the treatment of knee OA amongst 12 TCM hospitals in China.(Yao et al., 2005) An in vitro study (Yang et al., 2002) demonstrated that aqueous extract of Dang Gui could enhance the proliferation of human osteo-precursor cells and stimulate alkaline phosphatase (ALP) activity and synthesis of type I collagen which are involved in reducing pathological changes of articular cartilage and subchondral bone in OA.

Another effect of Dang Gui that has emerged during clinical practice and laboratory research recently is its antioxidant property. An in-vivo and in-vitro study using an endotoxin-induced mice model indicated an immune-supporting and protective action of an aqueous extract of Dang Gui against lethal systemic inflammatory diseases.(Wang et al., 2006) This kind of antioxidant protective effect could also be demonstrated in a rat study of gastric ulcer healing in which the extract from Dang Gui promoted migration of gastric epithelial cells and synthesis of mucus layer after injury.(Ye et al., 2003) The polysaccharide fraction of Dang Gui was regarded as the key component of its antioxidant activity, reducing reactive oxygen species (ROS) and activating T cells to enhance immunological protective activities.(Yang et al., 2006b, Yang et al., 2007b) Anti-oxidation activity was also found in the volatile oil of Dang Gui in addition to water-soluble antioxidant compounds such as polysaccharides and ascorbic acid.(Li et al., 2007b)

As a degenerative disease, OA is associated with mechanical stress of joints and dysfunction of articular cartilage, subchondral bone, ligaments, synovial membrane and periarticular muscles.(Henrotin and Kurz, 2007) Articular cartilage is particularly associated with oxygen tension due to aging. Oxygen tension can stimulate chondrocytes in articular cartilage, overproducing ROS and nitric oxide (NO), and then impairing matrix synthesis leading to degeneration and increasing pro-inflammatory cytokines, influencing the production of prostaglandins.(Fermor et al., 2007) Chondrocyte DNA experiments in articular cartilage from OA patients demonstrated the influence of oxidative damage in the pathogenesis of OA, and the serum antioxidative status of OA patients also demonstrated the relationship between oxidative stress and collagen

metabolism.(Altindag et al., 2007, Yudoh et al., 2005) Other studies suggest that intake of antioxidants may reduce the progress of pathogenesis of OA,(McAlindon et al., 1996b, Wang et al., 2007b) therefore the antioxidative action of Dang Gui could potentially play a key role in OA treatment.

Dang Gui is considered to be quite a safe herb with a long history of medical and dietary use in China. It is readily purchased over-the-counter in America too. The LD_{50} of oral Dang Gui extract has been found to be 100 g/kg in rats.(Thorne Research Inc., 2004)

8.4.2 Bai Shao

Bai Shao (*Radix Paeoniae Lactiflorae*) is the dried root of peony. Bai Shao has been widely used to soothe the Liver and invigorate the Blood circulation as well as relieve pain and cramps according to CM theory. The main bioactive component of Bai Shao is referred to as 'Total Glucosides of Paeony '(TGP), which includes paeoniflorin (PF), paeonin, hydroxyl-paeoniflorin, albiflorin, and benzoyl-paeoniflorin, with PF being the main principal constituent.(Zhu et al., 2006) PF has been reported to exhibit many pharmacological effects such as anti-inflammatory, anti-oxidative and anti-allergic effects, anti-hyperglycaemic and anti-hyperlipidemic effects, analgesic effects, neuromuscular blocking effects, cognition-enhancing effects and inhibitory effects on steroid protein binding.(Yang et al., 2004, Liu et al., 2006a, Lee et al., 2005) In experiments of collagen-induced arthritis of Sprague-Dawley (SD) rats, cytokines produced by fibroblast-like synoviocytes (FLS) could be inhibited by TGP; levels of prostaglandin E_2 (PGE_2) produced by FLS were decreased by TGP in vitro, and the level of cyclic adenosine monophospate (cAMP) was increased.(Chang et al., 2007) Another in-vitro experiment also showed that TGP could reverse the stimulation of tumour necrosis factor (TNF-α) on FLS, reducing the level of PGE_2 and interleukin-1 (IL-1β) and increasing depressed cAMP levels.(Zhang et al., 2007) Therefore, this kind of pharmacological effect is suitable for treatment of rheumatoid arthritis (RA) as RA is characterised by high levels of PGE2 in plasma and synovial fluid. TGP has been approved as an anti-inflammatory medication and an immunomodulator in China.

A randomised clinical trial (Xu et al., 2004) of TGP capsule compared with Nabumetone (NAB, a popular cyclooxygenase-2 inhibitor) in OA patients indicated that the symptoms of those in the treatment group had significantly improved after 6 weeks of treatment and that the VAS scores of pain associated with flat ground walking and the Likert scores of knee pain and lower limb function were significantly decreased compared with the control group ($p<0.01$). However another trial found there was no significant difference between the two groups ($p>0.05$) though both of them could improve symptoms effectively.(Xu et al., 2006) In addition, in this study there was no significant difference between the two groups in patient self-evaluation and the doctor's assessment of treatment. (Xu et al., 2006) As for monitoring of side-effects, a significantly higher percentage of participants in the NAB control group (32.5%) reported side-effects compared with the TGP treatment group (12.5%) ($p<0.05$). (Xu et al., 2006)

In another study, high levels of nitric oxide (NO) and its inducible nitric oxide synthetase (iNOS) were found in the joint fluid of OA patients. NO is a transmitter substance inhibiting synthesis of collagen and proteoglycan during OA development. The level of NO and iNOS in serum and joint fluid were significantly reduced after three months treatment with TGP Capsule ($p<0.01$) compared with the baseline.(Rao et al., 2006)

Bai Shao is considered a safe herb. An acute toxicity experiment (Li et al., 1991) indicated the median lethal doses (LD_{50}) of TGP administrated by intravenous (iv.) and intraperitoneal (ip.) in mice were 159 mg/kg and 230 mg/kg respectively; however, there was no cases of death during intragastric (ig.) application with 2500 mg/kg in 1 week, indicating that oral administration of TGP is a safe method. Chronic toxicity animal experiments in rats and dogs demonstrated no obvious changes in eating habits, weight, routine blood tests, routine urine tests and liver and kidney function tests with 90 days treatment, though they did find an increase in thrombocytes.(Li et al., 1991) This study also found no pathological change among 18 important organs including the heart, liver, kidney and brain in histopathology examinations.(Li et al., 1991) Collectively this evidence supports the contention that Bai Shao is a safe and low toxicity herb.

Modern research has also found the maximum tolerance dosage of Bai Shao granules solution for mice by intragastric application with 850% concentrated liquor was equal to

342.4g raw herb per kilogram, whilst the maximum dosage of the raw herb was 160g per kilogram if mice were given 400% concentrated Bai Shao decoction.(Zhang et al., 2006) This experiment demonstrated that the concentrated granules of Bai Shao had the same anti-inflammatory and analgesic effects as the raw herb, but the granules were more effective when it was administered at the same dose of the raw herb. Also it was safer than decoction (raw herbs) because of its higher maximum dosage.(Zhang et al., 2006)

8.4.3 Qin Jiao

Qin Jiao has been used for treatment of inflammatory diseases including OA and RA in CM. It has the actions of dispelling Wind and Dampness, soothing the sinews, purging heat and stopping pain according to CM theory. It is the root or bark of Gentianaceae (*Gentianae Macrophyllae Pall*). Its ethanol extract has an inhibitory effect on anthrax bacillus, staphylococci, typhoid bacillus, pneumococci, bacillus dysenteriae and vibrio comma.(Yu et al., 2004) The major constituents of Qin Jiao are gentiopicroside, swertamarin, and sweroside.(Yang et al., 2006a)

A study on the anti-inflammatory effects of its component gentiopicroside by intragastric administration indicated it could reduce xylene-induced auricle oedema of mice compared with the saline water and indomethacin (control) groups. ($p<0.01$) (Chen et al., 2003). The gentiopicroside lotion also significantly decreased the permeability of celiac blood capillaries induced by acetic acid in comparison with a saline water group and a prednisone control group. In addition, the number of times of body-twisting reaction was significantly less than in the saline water group ($p<0.05$) and the aspirin group ($p<0.01$). But there was no significant difference in the reduction of paw oedema induced by nystatin between the gentiopicroside group and the indomethacin group, though it was better than the saline water group. Therefore, the study showed the anti-inflammatory mechanism of gentiopicroside may be different to that of indomethacin. The animal experiment also demonstrated that gentiopicroside cannot protect the stability of lysosome membrane since the mechanism by which nystatin-induced inflammation is induced is via instability of the lysosome membrane, however the anti-inflammatory mechanism of gentianine may involve suppression of the production of TNF-α and IL-6.(Kwak et al., 2005)

In addition, gentiopicroside was also found to relieve carrageenan-induced paw inflammation of SD rats and zymosan A-induced paw oedema of Wistar rats ($p<0.01$), but there was no statistical difference between the placebo group and treatment group in the nystation-induced inflammatory model of Kunming mice.(Chen et al., 2003) Another experiment utilizing acetic acid-induced tests on mice also indicated that both aqueous extract and ethanol extract of Qin Jiao have an analgesic effect and that the effect could be enhanced by increased dose.(Cui et al., 1992)

Extracts of Qin Jiao have been found to inhibit COX-1 in a dose-effect relationship in an in-vitro experiment, and could also inhibit COX-2 except at a low dose (0.1 mg/ml). Thus part of its anti-rheumatic mechanism might be due to inhibition of lymphocyte proliferation and cyclooxygenase, especially COX-2.(Long and Qiu, 2004)

A pharmacokinetic experiment of gentiopicroside indicated its assimilation half-life was 1.0134 hours and elimination half-life was 6.727 hours, demonstrating that it belongs to the category of quick assimilation and slow elimination drug, indicating that it can keep a fair steady state in the body.(Wang et al., 1997) Furthermore, there was clear evidence of easy absorption as its maximum blood concentration was obtained at 1.0305 hour after intragastric application.(Wang et al., 1997)

8.4.4 Mu Li

In CM, Mu Li (oyster shell) is categorised as having a salty taste and being cold nature. It can calm ascending Liver Yang, relieve uneasiness of body and mind and dissipate nodules. As the shell of oyster, Mu Li is composed of mineral substances and very few organic materials, the majority of which is calcium carbonate (80-95%) with calcium phosphate and calcium sulphate as well.(Tan and Li, 1993, Zhang et al., 2004c)

Although OA is traditionally considered to be a disease of articular cartilage, there is increasing evidence that the bone is involved as well. A study supported the hypothesis that femoral bone from patients with OA has a reduced material density and appeared to be under-mineralised, with hardness values that were 7% lower than those from osteoporotic bone.(Coats et al., 2003) Research also suggests that bone resorption is increased in the presence of OA. (Hunter et al., 2003) It is known that calcium is the main

constituent of bone matrix and calcium is the main element of oyster shell; therefore, there is some logic to the application of Mu Li in OA. But the use of oyster shell in CM is not equivalent to the administration of calcium.

A Japanese experiment in ddY strain male mice (along with ICR strain mice) indicated that 1g/kg and 2g/kg doses of Mu Li could reduce number of times of body twisting induced by acetic acid, thus demonstrating its positive effect in analgesia.(Zhang, 1999)

An acute toxicity experiment (Ma et al., 2006) indicated that the LD_{50} of calcium of oyster shell was > 15g/kg for Kunming mice indicating that Mu Li is considered non-toxic. In addition, the rate of calcium retention of mice treated with oyster shell was higher than in a bio-calcium group, demonstrating that calcium from oyster shell could be absorbed more easily by the body.

8.4.5 Gan Cao

Gan Cao (liquorice root) is a widely used Chinese herb and is the root of *Glycyrrhiza*. In CM, Gan Cao is regarded as having the functions of tonifying Qi, clearing Heat, detoxification, eliminating phlegm, relieving pain and harmonising and moderating the properties of herbs within a medicinal formula. Liquorice has been used as a flavouring agent and expectorant in western countries. There are 84 groups of compounds that have been separated from Gan Cao to date, and flavonoids, triterpenes and polysaccharide substances are the major compounds.(Liang et al., 2006, Tian et al., 2006) Pharmaceutical research has concentrated on glycyrrhizic acid, glycyrrhetinic acid, isoflavonoid and flavonone in particular.

Many studies indicate that glycyrrhizic acid, glycyrrhetinic acid and derivatives of them have anti-bacterial, anti-viral, anti-anaphylaxis and hepato-protective functions and are able to improve immunologic function.(Li, 2004) Analyses has demonstrated that the flavonoid of Glycyrrhiza has antioxidative and antineoplastic effects.(Xing et al., 2003)

An acute toxicity test of mono-ammonium glycyrrhizinate, a derivative from glycyrrhizin, indicated that the LD_{50} and LD_0 for rabbits were 400mg/kg and 300mg/kg respectively;

the LD_{50} and LD_0 of accumulation toxicity were 300mg/kg.d and 200mg/kg.d respectively through intraperitoneal injection.(Bai et al., 2003)

8.4.6 Huai Niu Xi

Niu Xi is the root of a perennial herb (*Achyranthis Bidentatae*). The name literally means "ox knee" in Chinese, referring to the leaf node on the stem of the plant. There are two major species known as Niu Xi: one is Huai Niu Xi and another is Chuan Niu Xi, (*Radix Cyathula Officinalis*). Although they have similar actions, Huai Niu Xi (*Radix Achyranthis Bidentatae)* has been used more widely, particularly in the treatment of knee disease, because it is stronger than Chuan Niu Xi in tonifying the Liver and Kidneys and strengthening the sinews and bones which benefit the joints according to Chinese medicine theory. (Bensky et al., 2004)

The main actions of Huai Niu Xi include invigorating the Blood, dissipating Blood stasis, tonifying the Liver and Kidneys, strengthening the sinews and bones, and inducing the downward movement of Blood and fire, as well as directing other herbs to the lower back and lower limbs. Pharmacological studies and chemical analysis have found polysaccharides, phytoecdysones and triterpenoids saponins are the main compounds in Huai Niu Xi.(Meng and Li, 2001) In vitro studies indicated the extract of Huai Niu Xi has antitumor and immunomodulation functions, anti-viral, anti-inflammatory, anti-coagulation and anti-amnesia effects. (Li and Li, 1997, Yu and Zhang, 1995, Lu et al., 1999, Shao et al., 2002, Lu et al., 1997, Tang et al., 1996)

The polysaccharide isolated from Achyranthis Bidentatae is regarded as being responsible for the main pharmacodynamic actions of the herb. An animal experiment (Lin et al., 2003) showed the extract of Huai Niu Xi which was applied with saline solution by oral administration could reverse the shortened step-through latency (STL) of amnestic Sprange-Dawley rats induced by Dizocilpine (known as MK-801). According to CM, deficiency of the Liver and Kidneys is the main reason causing amnesia. This study suggested that Huai Niu Xi could enhance cognition which could be linked to the action of Huai Niu Xi tonifying the Liver and Kidneys.

The water extract of Huai Niu Xi has been observed reducing the writhing response of mice in hot plate or acetic acid induced tests and eliminating auricle oedema of mice induced by croton oil.(Lu et al., 1997) This indicates the anti-inflammation and analgesia effects of Huai Niu Xi. In addition, the ethanol extract of Achyranthis Bidentatae could also reduce the paw oedema of adjuvant arthritis rats and pathological changes of synovialis. (Zhao et al., 2008) A Korean study (Han et al., 2005) found the ethanol extract combination of Huai Niu Xi (Achyranthis Bidentatae) and Guan Cang Zhu (Atractylodes Japonica) had anti-inflammatory and analgesic effects on rheumatoid arthritis induced in mice and rats, but the active compound is still unclear.

8.4.7 Bai Shao combined with Gan Cao

Shao Yao Gan Cao Decoction, simply composed of Bai Shao and Gan Cao, is a classical and effective formula detailed in the ancient text the *Shang Han Lun* (*Discussion of Cold-Induced Diseases*) written almost 2000 years ago. This formula is efficacious in soothing the Liver and sinews, moderating spasm and relieving aches and is suitable for pain or stiffness of muscles or tendons and abdominal pain. In modern clinical practice, this formula is usually prescribed for lumbago, sciatica, epigastric pain, ischialgia, trigeminal neuralgia and facial spasm .(Cao et al., 2006a)

Animal experiments indicate that Shao Yao Gan Cao Decoction has analgesic and anti-inflammatory effects; this formula reduced the number of times of body twisting induced by acetic acid in mice had an analgesic rate of 58.85%, and eliminated xylene-induced auricle oedema with an efficacy of 45.68%.(Qiu et al., 1996) In a formaldehyde-induced pain model of Wistar rats,(Yan et al., 2001) Shao Yao Gan Cao Decoction inhibited pain with a dose-effect relationship either in Stage I (0-10min) or Stage II (10-60min), with Stage I relating to direct stimulation of peripheral nerves and Stage II stage referring to pain of spinal neurons owing to a secondary inflammatory reaction. Furthermore, this formula reduced the NO content of serum and spinal tissue in an acetic acid induced pain model of mice ($p<0.01$) (NO is regarded as an important messenger of pain transmission).(Yan et al., 2001) Another in-vivo study found that Bai Shao and Gan Cao decreased PGE_2 content and increased super oxide dismutase (SOD) of serum and spinal tissue of Kunming mice with a dose-effect relationship, and indicated that inhibition of

prostaglandin synthesis might be the mechanism of the analgesic effect of Shao Yao Gan Cao Decoction.(Feng et al., 2002)

As for the proportion of Bai Shao and Gan Cao in this formula, an experiment found there was the significant analgesic effect when the ratio of Bai Shao versus Gan Cao was 2:1, and that Zhi Gan Cao (cooked Gan Cao) was more suitable for analgesia. The feasible dose of this decoction for analgesic effect was 30-60g/kg/day for CFW mice.(Qin et al., 1997) The decoction of the combination of Bai Shao and Gan Cao was found to increase the solubility and utilisation ratio of paeoniflorin, glycyrrhizic acid and glycyrrhetinic acid compared with using single herbs. (Wang and Liu, 1999)

8.5 Potential drug-herb interactions

All of individual herbs in the Bai Niu capsule are legally available for use in Australia. Though the potential drug-herb interactions of this formula are still unknown, some research has indicated potential reactions of the component herbs with other western drugs or herbs. This information has informed the exclusion criteria used in this pilot study. Routine safety monitoring has therefore been conducted throughout clinical study.

It has been reported that Bai Shao has been associated with measles-like eruptions, pruritus, rashes and restlessness.(Bensky et al., 2004) Traditionally, it is contraindicated in combination with the herb Li Lu (*Veratrum nigrum Radix*). Bai Shao contains potassium so it is advised that it should not be used with potassium sparing diuretics as excessive potassium may result if taken together. (Chan and Cheung, 2000) In addition, vitamin C, nicotinic acid, giutamic acid, hydrochloric acid may destroy the glycoside activities of Bai Shao.(Chan and Cheung, 2000) An in- vitro study indicated that the pharmacokinetic parameters and bioavailability of paeoniflorin, the main ingredient of Bai Shao were markedly enhanced when co-administered with sinomenine (Qing Feng Teng, *Sinomenium acutum*).(Liu et al., 2005b)

Dang Gui has not been reported as causing major side effects following oral administration, however there have been some reports of mild lassitude, drowsiness and urticaria noted.(Bensky et al., 2004) Since this herb contains potassium, concurrent use with Antisterone, Spironolactone, Triamterene, or Amiloride may result in hyperkalemia,

and it may exaggerate the anticoagulation effect of warfarin.(Chan and Cheung, 2000) Phytochemical analysis found that Dang Gui consists of ferulic acid and several natural coumarin derivatives, and in- vivo and in- vitro studies have shown that ferulic acid has antithrombotic activity suggesting that Dang Gui may potentiate the risk of bleeding if combined with warfarin and NSAIDs.(Page and Lawrence, 1999, Abebe, 2002) Dang Gui also contains psoralen and bergapten which could theoretically increase the risk of phototoxicity when combined with drugs like sulfa or some natural products such as St. John's wort.(Scott and Elmer, 2002)

Qin Jiao traditionally should not be used in persons with loose stools/diarrhoea or incontinence of urine.(Bensky et al., 2004) Although its ethanol extract has anti-inflammatory activity which is comparable to that of prednisone,(Yu et al., 2004) the contraindications for the use of Qin Jiao and other concurrent medication are still unknown.

Mu Li may cause precipitation affecting the absorption of the drug, lowering the serum levels, and reducing the antibacterial effect if concurrently used with Tetracyclines.(Chan and Cheung, 2000) It can also reduce the pharmaceutical strength and therapeutic effect of prednisolone, isoniazid and laevodopa.(Chan and Cheung, 2000) Due to its calcium content, Mu Li may increase contraction of cardiac muscle with digitalis, and may reduce the effect of antibiotics like tetracyclines, kanamycin, neomycin.(Chan and Cheung, 2000)

Precipitations could be formed if Huai Niu Xi is used with potassium iodide, or sodium iodide due to the reaction between the alkaloid (from Huai Niu Xi) and iodine.(Chan and Cheung, 2000) In addition, Huai Niu Xi should not be taken with sodium bicarbonate, bismuth subcarbonate, ferrous sulfate, ferri ammoni cirtras, aluminium hydroxide, magnesium sulfate since it may cause precipitation.(Chan and Cheung, 2000) On the other hand, Huai Niu Xi contains glycoside, and acidic drugs including Vitamin C, nicotinic acid, glutamic acid, hydrochloric acid will reduce the glycoside activities of Huai Niu Xi and reduce its therapeutic effect.(Chan and Cheung, 2000)

Zhi Gan Cao is licorice root (Gan Cao) that is prepared with honey to enhance its tonifying effect. Gan Cao should not be combined with Jing Da Ji (*Euphorbiae*

pekinensis Radix), Gan Sui (*Kansui Radix*), Yuan Hua (*Genkwa Flos*) and Hai Zao (*Sargassum*) according to CM theory.(Bensky et al., 2004) This Chinese herb contains potassium so it should not be used with potassium sparing diuretics (such as Anisterone, Spironolactone), as excessive potassium may result if taken together.(Chan and Cheung, 2000) In addition, Triamterne, Amiloride. Quinine, Ephedrine, and Atropine will reduce the therapeutic effect of Gan Cao.(Chan and Cheung, 2000) The concurrent use of Gan Cao can reduce the absorption rate and reduce the effectiveness of drugs like erythromycin, chloramphenical, tetracyclines, isoniazid, and rifampicin.(Chan and Cheung, 2000) However, those interactions are based on single herbs. A study showed the aqueous licorice root extract reduced the toxicity of glycyrrhizin which may be due to the component interaction before and/or during intestinal absorption.(Cantelli-Forti et al., 1994) The oral administration of Gan Cao, a common herb used in medicinal formulae, is generally considered safe at recommended dosage levels. It should not be used long-term and in large doses in persons with hypertension.(Bensky et al., 2004)

8.6 Preparation of the study medicine

The Bai Niu Capsule is composed of the six Chinese herbs previously described. All are in common usage in Australia and China and are not listed on the National Standard for the Uniform Prescribing of Drugs and Poisons (SUSDP). The placebo capsules were filled with lactose USP (United States Pharmacopeia) grade for pharmaceutical use. The study medications were provided as soft gelatin capsules containing concentrated herbal granules or lactose.

The dosage of the study medications was five capsules taken three times a day, at least 30 minutes after food. This is equivalent to 7.5 grams of granules per day (either herb or placebo). According to the concentration technique, the ratio of herbal extracts and the excipient is 1:1.5, therefore the actual dosage of herbs per day in the treatment group is 3 grams, equivalent to 11.6 grams raw herb based on the actual concentration ratio 1:3.86. The study medications were manufactured in one batch by a Taiwanese pharmaceutical company which has the GMP (Good Manufacturing Practice) certification by the Australian Therapeutic Goods Administration (TGA), and then shipped (with certificates of analysis) and stored in the clinical trial pharmacy of the Alfred Hospital, Prahran,

Melbourne, Australia. Labelling was conducted by a third party which was not involved in the study. The investigational products were stored at <25°C as required in a secure area with access limited to the investigator(s) and pharmacy staff.

Chapter 9 Investigation Results of the Reliability of the Chinese Medicine Diagnostic Process

9.1 Introduction

As discussed in Chapter 6, to date no studies have systematically investigated the reliability of all four diagnostic methods used in the Chinese medicine (CM) diagnostic process (including CM Syndrome diagnosis). Only a few studies have assessed the reliability of CM diagnosis according to the Eight Guiding Principles. In addition, there are no published empirical studies that have established the CM Syndromes of OA. CM practitioners usually use CM diagnostic variables as evidence of change in clinical practice. If they are consistent, then these could be used in clinical trials as outcome indicators to assess the efficacy of CM therapies in addition to western medicine tools.

Therefore, this inter-rater reliability sub-study was conducted as part of a clinical trial into the efficacy of Chinese herbal medicine in the treatment of knee osteoarthritis (OA).

9.2 Study objectives

The study objectives were:

1. To investigate the degree of inter-practitioner consistency of:

    1.1 Clinical variables in a CM examination using the four diagnostic methods: inquiry, inspection, auscultation and palpation;

    1.2 CM Syndrome diagnosis according to the Eight Guiding Principles

    1.3 CM Syndrome diagnosis according to Zang-Fu Theory

2. To provide empirical data on CM Syndromes of OA

9.3 Hypotheses

The study had the following null hypotheses:

1. The level of agreement between two CM practitioners will be low for clinical diagnostic variables in a Chinese medicine examination using the four diagnostic methods of inquiry, inspection, auscultation and palpation.

2. The inter-rater reliability between CM two practitioners will be low for CM Syndrome diagnosis based on the Eight Guiding Principles.

3. The level of agreement between two practitioners will be low for CM Syndrome diagnosis according to Zang-Fu Theory.

4. There will be no clearly discernible CM Syndromes of OA

9.4 Materials and methods

This sub-study was part of the clinical trial to assess the efficacy of a Chinese herbal medicine treatment for OA of the knee. For a more detailed description of the methods used, refer to Chapter 7.

9.4.1 Practitioners

Two CM practitioners participated in this study. Both are registered CM practitioners in the state of Victoria, Australia, with Bachelor Degree level training in CM. One practitioner (Practitioner A, the author of this thesis) completed his CM training (Bachelor and Masters Degrees) in a university in China and has ten years clinical experience working in CM hospitals in China. The other practitioner (Practitioner B) completed her CM training in Australia with an internship in China, and has been in clinical practice in Australia for over ten years.

9.4.2 Study participants

This was a sub-study of a clinical study into knee OA. The inclusion criteria included unilateral or bilateral OA of the knee and fulfilment of the criteria provided by the American College of Rheumatology (ACR) 1995,(Hochberg et al., 1995) mainly based on knee pain and presence of radiographic osteophytes. Radiographic evidence of OA was based on the Kellgren-Lawrence radiographic system,(Kellgren and Lawrence, 1957) either grade II or grade III severity primary tibio-femoral OA as a condition of inclusion.

The exclusion criteria of the study included secondary OA or rheumatoid inflammatory or any other type of arthritis, accompanying OA of hip of sufficient severity to interfere with the functional assessment of the knee, having received intra-articular treatment of the involved joint or joint lavage in the previous 6 months (e.g., corticosteroids or hyaluronic acid) or knee surgery during the previous 3 months, and any significant systemic illnesses or medical conditions that could lead to difficulty complying with the protocol.

There was no CM assessment or CM Syndromes diagnosis made prior to the study.

9.4.3 Methods of data collection

9.4.3.1 The Four Diagnostic Methods assessment

A CM assessment form was utilised to systematically record CM diagnostic information during a CM examination, derived from the four diagnostic methods: inquiry, inspection, auscultation/olfaction, and palpation. In addition, there was a diagnosis summary section that included the Eight Guiding Principles and CM Syndrome diagnosis according to Zang-Fu Theory). This is described in the Methods Chapter. The CM assessment form can be found in Appendix 8.

The CM assessment form was originally developed by O'Brien and colleagues,(O'Brien et al., 2009a, O'Brien et al., 2009b) but further developed to include a special section relating to the signs and symptoms of OA of the knee. The investigated endpoints are set out in Table 9.1. In the Inquiry section, several questions initially asked the practitioner to record the presence or absence of a particular sign or symptom. If present, further (more detailed) questions were asked. The sense of olfaction is seldom used nowadays (though it was a diagnostic method used ancient times) therefore olfaction was not used in this study.

There are 28 different kinds of pulses according to CM theory and each of them has different characteristics and indicate particular pathology.(Deng et al., 1984) However, only the three basic characteristics of pulse (force, depth and speed) were assessed in this study to simplify the investigation.

Table 9.1 Chinese medicine diagnostic endpoints

Diagnostic method	Diagnostic variables	Investigated endpoints	Response options
Inquiry	Body temperature	Presence of chills	Yes; No
		Severity of chills	Slight; Moderate; Strong
		Presence of cold	Yes; No
		Severity of cold	Slight; Moderate; Very
		Presence of cold hands and feet	Yes; No
		Severity of cold hands and feet	Slight; Moderate; Very
		Presence of the sensitivity to cold	Yes; No
		Severity of the sensitivity to cold	Slight; Moderate; Very
		Presence of the sensitivity to heat	Yes; No
		Severity of the sensitivity to heat	Slight; Moderate; Very
		Presence of fever	Yes; No
		Timing of fever	Constant; Alternating
		Severity of fever	Slight; Moderate; Strong
	Sweat	Presence of spontaneous sweating	Yes; No
		Severity of spontaneous sweating	Slight; Moderate; Heavy
		Presence of night sweating	Yes; No
		Severity of night sweating	Slight; Moderate; Heavy
	Headache	Presence of headache	Yes; No

		Location	Left; Right; Back; Forehead; Top
		Onset time	Morning; Afternoon; Evening; Anytime
		Type	Throbbing; Distending; Pressure; Moving; Dull
		History	<2 weeks; 2-4 weeks; 1-3 months; 3-6 months; >6 months
	Dizziness	Presence of dizziness	Yes; No
		Onset time	Morning; Afternoon; Evening
		Onset frequency	Daily; every 2-3 days; every 4-6 days; weekly; fortnightly; monthly; 3 monthly; 6 monthly
		History	<2 weeks; 2-4 weeks; 1-3 months; 3-6 months; >6 months
	Body parts	Presence of numbness	Yes; No
		Location of numbness	R fingers; R hand; R arm; R toes; R foot; R leg; L fingers; L hand; L arm; L toes; L foot; L leg; Face; Head; Neck; Upper back; Mid-back; Lower back; Hips
		Presence of body pain	Yes; No

		Location of body pain	R fingers; R hand; R elbow; R arm; R toes; R foot; R knee; R leg; R face; R neck; R upper back; R mid-back; R lower back; R hip; L fingers; L hand; L elbow; L arm; L toes; L foot; L knee; L leg; L face; L neck; L upper back; L midback; L lower back; L hip;
	Urine	Colour	Clear; Light yellow; Dark yellow
		Quantity	Little; Moderate; Large
		Frequency	Normal; Frequent
		Night urination	Yes; No
		Burning Sensation	Yes; No
		Incomplete sensation	Yes; No
		Leakage	Yes; No
	Stools	Frequency of defecation	<1; day; 1-2; day; >2; day
		Quality of stools	Watery; Loose; Soft; Firm; Hard; Alternating loose and hard
		Presence of constipation	Yes; No
	Appetite	Level of appetite	Poor; Good; Excessive
		Taste in the mouth	No; Sweet; Salty; Bitter; Sour; Pungent; Bland; Greasy; Inability to taste
		Sensation after eating	Normal; Nauseous; Bloated; Belching; Tired
	Thirst	Presence of thirst	Yes; No; Yes but no desire to drink
	Chest	Abnormal sensation	Yes; No

		Cough phlegm	Yes; No
	Abdomen	Presence of abdominal pain	Yes; No
		Location	Upper; Centre; Lower; Left side; Right side; Moving
		Quality	Stabbing; Distending; Spasms; Other
		Pain aggravated by heat	Yes; No; Don't know
		Pain aggravated by pressure	Yes; No; Don't know
		Pain relieved by heat	Yes; No; Don't know
		Pain relieved by pressure	Yes; No; Don't know
		Presence of bloating	Yes; No
	Ears and eyes	Hearing	Normal; Slight decrease; Significant decrease
		Presence of tinnitus	Yes; No
		Presence of blurred vision	Yes; No
		Presence of dry eyes	Yes; No
		Presence of watery eyes	Yes; No
		Presence of sensitivity to light	Yes; No
		Presence of sensitivity to wind	Yes; No
	Sleep	Quality	Poor; Good; Very Good
		Dreaming	No; Seldom; Occasional; Frequent
		Difficulty falling asleep	Yes; No
		Waking up at night	Yes; No
	Energy	Energy level	Little; Moderate; Abundant

	Breath	Presence of shortness of breath	Yes; No
	Emotions	Emotions experienced over the past week	Calm; Anxiety; Excessive thinking; Irritability; Sadness; Fearfulness; Excessive happiness
	For women	Status of menopause	Yes: No
	Knee joints	Presence of knee pain	Yes: No
		Affected knee	Right; Left; Both
		Pain duration	Constant; Variable; Moving
		Pain quality	Throbbing; Heavy; Dull; Burning; Grinding
		Weather which affected pain	No; Cold; Damp; Windy; Hot
		Presence of knee stiffness	Yes; No
		Onset time of stiffness	Morning; Afternoon; Evening; Occasional
		Stiffness duration	<30 minutes; 30 minutes to several hours; All the time
		Presence of knee swelling	Yes; No
		Swelling location	Right; Left; Both
		Swelling sensation	No; Hot; Cold; Other
		Swelling history	<2 weeks; 2 weeks to 1 month; 2-6 months; > 6 months
		Status of knee strength	Normal; Weaker but doesn't affect activities; Weaker and affects activities; Need assistance
		Knee weakness history	< 1 month; 2-6 months; 6-12 months; >1 year

		Presence of muscle atrophy	No; Little; Notable
Inspection	Spirit	Strength	Poor; Moderate; Strong
	Complexion	Colour	Normal; Yellow; Pale; Red; Green; Black
		Lustre	Dry; Moist
	Hair	Amount	Plentiful; Thinning; Receding forehead; Balding
		Appearance	Dry; Lustrous
	Physical build	Body frame	Small; Medium; Large
		Musculature	Muscular; Flaccid
		Body fat	Underweight; Moderate weight; Overweight
	Posture	Sitting posture	Upright; Slumped
		Walking posture	Restricted; Unrestricted
	Tongue body	Size	Small; Moderate; Swollen; Thin
		Teeth marks	Yes; No
		Colour	Pale; Pink; Red/Crimson; Purple
		Red tip	Yes; No
		Constitution	Soft; Firm
		Cracks	Yes; No
		Spots	Yes; No
		Trembling	Yes; No
		Deviation	Yes; No
	Tongue coating	Presence	Yes; No
		Thickness	Absent; Very thin; Thin; Thick

		Quality	Dry; Moist; Sticky; Curdy; Peeled
		Colour	White; Yellow; Grey; Green; Black
	Lips	Colour	Pale; Pink/Red; Bright red; Purple
Auscultation	Voice	Strength of voice	Soft; Moderate; Loud
	Breath sounds	Characteristics of sounds	Normal/Silent; Wheezing; Heavy
Palpation	Pulse	Speed (Left)	Slow; Moderate; Fast
		Location (Left)	Superficial; Mid-level; Deep
		Force (Left)	Weak; Moderate; Forceful
		Speed (Right)	Slow; Moderate; Fast
		Location (Right)	Superficial; Mid-level; Deep
		Force (Right)	Weak; Moderate; Forceful
	Hands	Temperature	Cold; Warm; Hot
		Moisture	Sweaty; Neither sweaty nor dry; Dry

9.4.3.2 Eight Guiding Principles assessment

Practitioners were required to analyse the signs and symptoms according to the Eight Guiding Principles theory and indicate which option of each pair characterised that participant's condition. There are four pairs of principles that summarise the characteristics of the Syndrome(s) of each participant: Interior/Exterior, Heat/Cold, Excess/Deficiency and Yin/Yang. For the pair 'Interior/Exterior', however, the additional option for location of 'Semi-Interior/Semi-Exterior' was added. In addition, the degree of Heat/Cold and Excess/Deficiency were also assessed for these two principles. There were three grades: slight, moderate and strong.

9.4.3.3 CM Syndrome diagnosis assessment

Practitioners were required to formulate a specific CM Syndrome diagnosis according to Syndrome Differentiation which is mainly based on Zang-Fu Theory (see Chapter 2). There was no fixed list of possible CM Syndromes of knee OA provided. Practitioners were asked to draw a conclusion about the CM Syndrome diagnosis as in real clinical practice: an open-ended choice. Practitioners were also required to list which internal (Zang-Fu) organs were involved in the pathogenesis of the CM Syndrome for each participant, and to rank the order of importance of clinical signs or symptoms that led them to the final CM Syndrome diagnosis.

9.4.4 Study procedure

The inter-rater reliability study was conducted at the first study visit of the Chinese herbal medicine trial (the randomisation visit). Both practitioners conducted an entire CM assessment on the same day without any discussion before or after the assessment. Practitioner A (the Ph.D candidate) also conducted other assessments at this visit related to the Chinese herbal medicine study. Practitioner B conducted the CM assessment only. There was a maximum 30 minutes between the two CM assessments conducted for each participant and each session lasted approximately 30 minutes. There was no training or discussion between the two practitioners prior to the CM assessment.

9.5 Statistical analysis

The level of agreement (percentage agreement) was calculated for each CM diagnostic variable assessed, and the CM Syndrome diagnoses according to the Eight Guiding Principles and Zang-Fu Theory. The (Cohen's) Kappa coefficient was applied for all sections of the Four Diagnostic Methods (Inquiry, Inspection, Auscultation and Palpation) and the Eight Guiding Principles. The Kappa coefficient is a statistical measure of inter-rater agreement for qualitative (categorical) items, which takes into account the agreement occurring by chance. It is considered a particularly conservative measure of level of agreement.

The interpretation of Kappa values used in this study is based on the work of Landis and Koch (see Table 9.2) (Landis and Koch, 1977). The Kappa is always less than or equal to 1. A value of 1 implies perfect agreement and values less than 1 implies less than perfect agreement.

Table 9.2 Interpretation of Kappa values

Kappa value	Strength of agreement
<0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost perfect

9.5.1 The Four Diagnostic Methods

The level of agreement for the key Inquiry endpoints was calculated, along with the Kappa coefficient. In the case of some Inquiry sub-questions (eg. when presence of a symptom was indicated, requiring further questioning about the nature of that symptom), where there were few responses (in the affirmative), the Kappa coefficient was not calculated.

9.5.2 Definition of agreement for the Eight Guiding Principles

The Eight Guiding Principles are four pairs of principles: Interior/Exterior (with the addition of Semi-Interior/Semi-Exterior), Heat/Cold, Excess/Deficiency and Yin/Yang. The criterion for agreement on each of the pairs of principles was strict agreement. For example, strict agreement on the location of Syndrome was defined as agreement on one of three possibilities: Interior, or Exterior, or Semi-Interior/Semi-Exterior. If one practitioner recorded ‘Interior’ and the other ‘Semi-Interior/Semi-Exterior’ this was not

considered a match. A diagnosis of ‘Heat’ by Practitioner A, for an instance, and ‘Heat and Cold’ by Practitioner B is deemed a disagreement.

9.5.3 Definition of agreement of the Zang-Fu Organ involvement and Syndrome diagnosis

In real practice, practitioners may diagnose more than one CM Syndrome and some syndromes may be dual diagnoses, for example ‘Kidney and Spleen Yang Deficiency’. For ease of analysis, all multi-CM Syndrome diagnoses were separated into individual CM Syndrome components based on the Zang Fu theory. For example, if a participant was diagnosed as Qi Deficiency of the Spleen and Kidney, then this diagnosis was separated into Qi Deficiency of the Spleen and Qi Deficiency of the Kidney. The level of agreement was then calculated as follows: exact agreement is defined as both practitioners listing exactly the same component Syndrome diagnoses and partial agreement is defined as an overlap (agreement) of at least one Syndrome diagnosis between the two practitioners. For example, if one practitioner wrote a diagnosis of Spleen Qi Deficiency and Kidney Yang Deficiency, and the other practitioner diagnosed Spleen Qi Deficiency and Heart Qi Deficiency, then there is partial agreement on one syndrome, that is, Spleen Qi deficiency.

In addition, practitioners were asked to list the involved Zang and Fu Organs. Level of agreement between the practitioners was assessed. Strict agreement was defined as the exact agreement on involved Zang (or Fu) organs for a participant. Partial agreement refers to an overlap of at least one Zang or Fu Organ between the two practitioners, that is, their list of involved organs had at least one in common.

9.6 Results

A total of 40 study participants were recruited in this inter-rater reliability study: 23 females and 17 males. The mean age of participants was 62.2 years (SD = 11.0) and the age range was 42 years to 92 years of age.

9.6.1 Reproducibility of key diagnostic variables

The reproducibility of the key Inquiry variables is set out in Table 9.3. The reproducibility of the key Inspection, Auscultation and Palpation variables is set out in Table 9.4.

9.6.1.1 Inquiry variables

There were 84 investigated endpoints in the Inquiry section covering the majority of elements taken in a case history. Inter-rater reliability was assessed for the 75 key inquiry variables and ranged from ‘poor’ to ‘almost perfect’ using the definition of Landis and Koch.(Landis and Koch, 1977) Results are set out in Table 9.3.

‘Almost prefect’ agreement was found in 18 variables, ‘substantial agreement ‘ was found in 16 variables, moderate agreement in 7 variables, and ‘fair agreement’ was found in 9 variables. ‘Poor’ agreement was only found in one variable, the sensation of incomplete urination. However, caution should be taken in the interpretation of agreement by Kappa in this case because of skewing of a high number of responses towards one particular response option. Therefore, the Kappa value was -0.06 even though the level of agreement was 87.5%. This is one of the limitations of the Kappa coefficient.(Crewson, 2005)

There are 23 variables which could not be analysed using the Kappa coefficient due to missing data in at least one of the tabulation cells, mainly due to the fact that one particular response was recorded consistently for a particular variable for one of the practitioners. For example, one practitioner recorded that none of the participants had fever while the other practitioner recorded one case of presence of fever. Therefore, the Kappa statistic cannot be calculated for this variable analysis even though its level of agreement is quite high, 97.5%. In addition, cases where the presence of a particular symptom necessitated a further set of choices about quality of that symptom was not high and correspondingly the number of analysable cases for the second set of choices was low, thus Kappa was not applied.

Table 9.3 Reproducibility of key Inquiry variables

Investigated endpoints		Valid cases (n)	Level of Agreement (%)	κ of result	κ SE (κ 95% CI)	Interpretation of κ
Presence of chills		40	80.0	0.23	0.19 (-0.13-0.60)	Fair
Presence of cold		31	70.0	0.35	0.29 (-0.22-0.92)	Fair
Presence of cold hands and feet		40	87.5	0.68	0.13 (0.44-0.93)	Substantial
Presence of the sensitivity to cold		38	85.0	0.73	0.12 (0.49-0.97)	Substantial
Presence of the sensitivity to heat		40	82.5	0.63	0.12 (0.39-0.88)	Substantial
Presence of fever		40	97.5	¶		
Presence of spontaneous sweating		40	87.5	0.73	0.11 (0.52-0.94)	Substantial
Presence of night sweating		40	90.0	0.76	0.11 (0.55-0.98)	Substantial
Presence of headache		40	97.5	0.94	0.06 (0.83-1.05)	Almost perfect
If yes	Location	12	75.0	*		
	Onset time	12	83.3	*		
	Type	12	58.3	*		
	History	12	75.0	*		
Presence of dizziness		40	95.0	0.86	0.10 (0.66-1.05)	Almost perfect
If yes	Onset time	3	66.7	*		
	Onset frequency	7	42.9	*		
	History	8	37.5	*		

Presence of numbness		40	97.5	0.95	0.05 (0.84-1.05)	Almost perfect
If yes	Location of numbness	14	28.6	*		
Presence of body pain		40	95.0	0.48	0.31 (-0.12-1.08)	Moderate
If yes	Location of body pain	37	43.2	*		
Urine colour		40	85.0	0.72	0.10 (0.52-0.92)	Substantial
Urine quantity		40	92.5	0.68	0.17 (0.35-1.02)	Substantial
Urine frequency		40	75.0	0.40	0.14 (0.13-0.68)	Fair
Night urination		40	92.5	0.82	0.10 (0.62-1.01)	Almost perfect
Urine burning Sensation		40	100.0	1.00	0.00 (1.00-1.00)	Almost perfect
Urine incomplete sensation		40	87.5	-0.06	0.03 (-0.12-0.00)	Poor
Urine leakage		40	90.0	0.78	0.10 (0.57-0.98)	Substantial
Frequency of defecation		40	87.5	0.72	0.12 (0.49-0.95)	Substantial
Quality of stools		40	70.0	0.58	0.10 (0.39-0.77)	Moderate
Presence of constipation		40	95.0	0.84	0.11 (0.63-1.05)	Almost perfect
Level of appetite		40	95.0	0.48	0.31 (-0.11-1.08)	Moderate
Taste in the mouth		40	97.5	0.87	0.12 (0.64-1.09)	Almost perfect
Sensation after eating		40	90.0	¶		
Presence of thirst		40	65.0	0.38	0.13 (0.12-0.65)	Fair
Abnormal chest sensation		40	95.0	0.72	0.18 (0.37-1.08)	Substantial

Cough phlegm		34	85.0	1.00	0.00 (1.00-1.00)	Almost perfect
Presence of abdominal pain		40	95.0	0.84	0.11 (0.63-1.05)	Almost perfect
If yes	Location	7	57.1	¶		
	Quality	7	28.6	¶		
	Pain aggravated by heat	7	42.9	¶		
	Pain aggravated by pressure	7	57.1	0.36	0.27 (-0.16-0.89)	Fair
	Pain relieved by heat	7	57.1	0.32	0.28 (-0.23-0.88)	Fair
	Pain relieved by pressure	7	71.4	0.56	0.27 (0.04-1.08)	Moderate
	Presence of bloating	7	85.7	¶		
Hearing		40	95.0	0.91	0.06 (0.80-1.03)	Almost perfect
Presence of tinnitus		40	92.5	0.76	0.13 (0.50-1.01)	Substantial
Presence of blurred vision		40	92.5	0.69	0.19 (0.33-1.05)	Substantial
Presence of dry eyes		39	97.5	0.93	0.07 (0.80-1.06)	Almost perfect
Presence of watery eyes		40	92.5	0.82	0.10 (0.62-1.01)	Almost perfect
Presence of the sensitivity to light		39	85.0	0.74	0.11 (0.53-0.95)	Substantial

Presence of the sensitivity to wind		40	95.0	0.88	0.08 (0.72-1.04)	Almost perfect
Sleep quality		40	77.5	0.81	0.11 (0.60-1.03)	Almost perfect
Sleep dream		40	75.0	0.61	0.10 (0.41-0.81)	Substantial
Difficulty to fall asleep		40	92.5	0.84	0.09 (0.66-1.01)	Almost perfect
Waking up at night		40	90.0	0.66	0.15 (0.36-0.96)	Substantial
Energy level		40	80	0.54	0.14 (0.27-0.82)	Moderate
Presence of the shortness of breath		40	90.0	0.66	0.16 (0.35-0.96)	Substantial
Experienced emotions over the past week		39	66.7	¶		
Status of menopause		21	100.0	1.00	0.00 (1.00-1.00)	Almost perfect
Presence of knee pain		40	95.0	¶		
If yes	Affected knee	38	94.7	0.92	0.06 (0.08-1.03)	Almost perfect
	Pain duration	38	71.1	¶		
	Pain quality	38	63.2	¶		
	Affected weather	38	68.4	¶		
Presence of knee stiffness		40	90.0	0.28	0.26 (-0.23-0.79)	Fair
If yes	Onset time of stiffness	35	68.6	¶		

	Stiffness duration	34	73.5	0.51	0.12 (0.26-0.75)	Moderate
Presence of knee swelling		40	95.0	0.90	0.07 (0.76-1.03)	Almost perfect
If yes	Swelling location	21	47.6	0.22	0.17 (-0.10-0.55)	Fair
	Swelling sensation	21	85.7	¶		
	Swelling history	21	95.2	¶		
Status of knee strength		39	71.8	0.27	0.15 (-0.02-0.57)	Fair
If yes	Weakness history	33	72.7	¶		
	Presence of muscle atrophy	33	69.7	0.51	0.13 (0.26-0.76)	Moderate

Key:

¶ Data missing from at least one tabulation cell, so Kappa unable to be calculated

SE – Standard Error; CI - Confidence Interval

9.6.1.2 Inspection variables

Agreement for the 24 Inspection diagnostic variables ranged from ‘poor’ to ‘moderate’. ‘Moderate’ agreement was found for two variables, ‘fair’ agreement was found for six variables, and ‘slight’ agreement was found for six variables. ‘Poor’ agreement was found for one variable, presence of tongue coating, though the level of agreement was 90.0%. This is because the data is skewed in the 2x2 response tabulation for calculating Kappa: the two practitioners both rated one participant each without presence of tongue coating but not the same patient. Although the data could still be theoretically calculated by Kappa, it led to a large difference in the interpretations between percentage agreement (high percentage agreement) and the Kappa value (very low). As previously stated, this is one of the limitations of the Kappa coefficient.(Crewson, 2005)

There are also nine variables which could not be analysed by Kappa due to one rater consistently choosing the one response. For example, one practitioner rated all of participants as having 'normal' complexion colour, but the other practitioner recorded other colours as well. However the level of agreement is reasonable (72.5%) for this endpoint. A similar result can be found for appearance of hair (67.6% agreement), sitting posture (97.5% agreement), presence of spots on tongue (95.0% agreement), presence of tongue trembling (77.5% agreement), presence of tongue deviation (85.0% agreement), constitution of tongue body (17.5% agreement), and colour of lips (85.0% agreement). In addition, practitioners could and did choose more than one response for the variable of quality of tongue coating, so the endpoint was only assessed by the level of agreement (based on the strict agreement criterion) (47.2% agreement). In addition, one of the response cells to calculate Kappa remained empty for one practitioner therefore Kappa could not be calculated. See Table 9.4 for more details.

9.6.1.3 Auscultation variables

Agreement between two practitioners for the two diagnostic auscultation variables was 82.5% for voice strength and 97.5% for the characteristics of breath sounds. Since one practitioner consistently chose the same responses for each participant for these variables, the Kappa statistics could not be applied. Results are set out in Table 9.4.

9.6.1.4 Palpation variables

Agreement ranged from 'poor' to 'substantial' for the eight investigated palpation endpoints. The results are set out in Table 9.4.

'Fair' agreement was found for the variable of the location of right pulse. 'Slight' agreement was found for four variables of pulse diagnosis, including the location of left pulse, the force of left pulse, the force of right pulse, and the speed of right pulse. A 'poor' level of agreement was found for the variable of the speed of left pulse, despite the percentage agreement being 76.9%. However this result of statistics should be interpreted carefully due to fact that responses were almost identical for each participant for one of the practitioners.

The variable of moisture of hands could not be analysed using the Kappa coefficient due to the fact that one practitioner consistently chose the same response.

Table 9.4 Reproducibility of inspection, auscultation and palpation variables

Investigated endpoints	Valid cases (n)	Level of Agreement (%)	κ of result	κ SE (κ 95% CI)	Interpretation of κ
Strength of spirit	40	52.5	0.07	0.08 (-0.09-0.24)	Slight
Colour of complexion	40	72.5	¶		
Skin lustre	25	68.0	0.14	0.13 (-0.11-0.39)	Slight
Amount of hair	40	75.0	0.54	0.11 (0.33-0.75)	Moderate
Appearance of hair	37	67.6	¶		
Body frame	40	72.5	0.47	0.13 (0.21-0.73)	Moderate
Musculature	40	60.0	0.05	0.11 (-0.18-0.27)	Slight
Body fat	40	67.5	0.39	0.13 (0.14-0.64)	Fair
Sitting posture	40	97.5	¶		
Walking posture	40	50.0	0.10	0.09 (-0.07-0.27)	Slight
Tongue size	40	52.5	0.15	0.12 (-0.08-0.38)	Slight
Presence of teeth marks on tongue	37	62.2	0.24	0.16 (-0.07-0.54)	Fair
Tongue colour	39	35.9	0.11	0.10 (-0.09-0.30)	Slight
Presence of red tip on tongue	39	74.4	0.22	0.13 (-0.04-0.48)	Fair
Tongue constitution	40	17.5	¶		
Presence of cracks on tongue	40	60.0	0.26	0.12 (0.02-0.50)	Fair
Presence of spots on tongue	40	95.0	¶		

Presence of tongue trembling	40	77.5	¶		
Presence of tongue deviation	40	85.0	¶		
Presence of tongue coating	40	90.0	-0.04	0.03 (-0.10-0.02)	Poor
Thickness of tongue coating	40	47.5	0.22	0.11 (0.00-0.44)	Fair
Quality of tongue coating	36	47.2	¶		
Colour of tongue coating	37	64.9	0.34	0.12 (0.09-0.58)	Fair
Colour of lips	40	85.0	¶		
Strength of voice	40	82.5	¶		
Character of breathing sounds	40	97.5	¶		
Pulse speed (left)	39	76.9	-0.05	0.03 (-0.12-0.01)	Poor
Pulse location (left)	40	65.0	0.20	0.15 (-0.11-0.50)	Slight
Pulse force (left)	40	42.5	0.08	0.10 (-0.11-0.28)	Slight
Pulse speed (right)	40	77.5	0.11	0.16 (-0.20-0.42)	Slight
Pulse location (right)	40	67.5	0.31	0.14 (0.03-0.59)	Fair
Pulse force (right)	40	42.5	0.13	0.10 (-0.08-0.33)	Slight
Temperature of hands	40	95.0	0.66	0.32 (0.03-1.28)	Substantial
Moisture of hands	40	82.5	¶		

Key: ¶ Data missing from at least one tabulation cell, so Kappa unable to be calculated

SE – Standard Error; CI - Confidence Interval

9.6.2 Reproducibility of the Eight Guiding Principles

Agreement was 97.5% for the variable pair of Interior/Exterior. The Kappa coefficient was unable to be applied as one practitioner consistently chose one response only. The majority of participants were categorised as having an 'Interior' condition. A similar finding also can be seen in terms of agreement on the Yin/Yang pair of principles. Although the level of agreement was 67.5% using the level of strict agreement, one practitioner gave a Yin Principle diagnosis for all 40 participants whilst the other practitioner rated 27 OA participants (67.5% of all participants) as Yin, so the Kappa coefficient was unable to be calculated for this pair.

'Slight' agreement was found for the Heat/Cold pair with the level of agreement being 32.5%. The level of agreement for the Excess/Deficiency pair was 77.5%, but it was interpreted as 'poor' agreement according to Landis and Koch's interpretation. This is because one practitioner diagnosed the majority OA participants (39 cases) as Deficiency, while the other practitioner rated 32 participants (80% participants) as Deficiency.

See Table 9.5 for more details.

Table 9.5 Reproducibility of the variables of the Eight Guiding Principles

Investigated endpoints	Valid cases (n)	Level of Agreement (%)	κ of result	κ SE (κ 95%CI)	Interpretation of κ
Interior / Exterior	40	97.5	¶		
Heat / Cold	40	32.5	0.08	0.05 (-0.02-0.18)	Slight
Excess / Deficiency	40	77.5	-0.05	0.04 (-0.13-0.04)	Poor
Yin / Yang	40	67.5	¶		

Key: ¶ Data missing from at least one tabulation cell, so Kappa unable to be calculated

SE – Standard Error; CI - Confidence Interval

9.6.3 Reproducibility of Zang-Fu Organ involvement, Meridians and CM Syndrome diagnosis

There was missing data in the sections of involved Fu Organs and CM Syndrome Diagnosis, so valid cases for reliability assessments were 31 and 39 respectively.

An overall summary of the level of agreement for Zang-Fu Organ involvement, Meridians diagnoses, and CM Syndrome Diagnosis is set out in Table 9.6 below.

Table 9.6 Level of agreement for involved Zang Fu Organs, Meridians and CM Syndrome diagnosis

Investigated variables		Zang Organs involved	Fu Organs involved	Meridians	CM Syndrome Diagnoses
No. of Valid cases		40	31	40	39
Mean number	Dr. A	2.4	1.3	2.0	2.0
	Dr. B	2.6	1.5	2.0	2.9
Level of agreement - strict agreement criterion (%)		12.5	22.6	15.0	0.0
Level of agreement - partial agreement criterion (%)		95.0	51.6	75.0	50.0

9.6.3.1 Zang Fu Organ involvement

The level of strict agreement was low but a higher level of agreement would have been found if these variables were assessed by partial agreement. For Zang and Fu Organs, the level of strict agreement between two practitioners was 12.5% and 22.6% respectively, and for partial agreement, this increased to 95.0% and 51.6% respectively.

There was only a slight difference between practitioners in the mean number of organs diagnosed as being involved. The mean number of Zang and Fu Organs diagnosed as being involved by Practitioner A was 2.4 Zang organs and 1.3 Fu organs and for Practitioner B, 2.6 Zang organs and 1.5 Fu organs.

The most commonly involved Zang Organs diagnosed by the Practitioner A were Kidney (75.0%), Spleen (65.0%) and Liver (62.5%), while for Practitioner B these were Kidney (95.0%), Liver (65.0%) and Spleen (42.5%). Level of agreement between the two practitioners on Kidney, Liver and Spleen involvement was 70.0%, 42.5% and 35.0% respectively, using a partial agreement definition.

The most commonly involved Fu Organs diagnosed by Practitioner A were Bladder (45.2%), Stomach (32.3%) and Large Intestine (29.0%), and for Practitioner B, Stomach (35.5%), Large Intestine (32.3%) and Gallbladder (32.3%). Agreement on involvement of Stomach, Large Intestine, Bladder and Gallbladder was 19.4%, 12.9%, 12.9% and 16.1% respectively based on a partial agreement definition.

See Table 9.6, Table 9.7 and Table 9.8 for more details.

Table 9.7 Ranking of most commonly involved Zang and Fu Organs

Rank	Zang Organ		Fu Organ	
	Cases diagnosed by Dr. A (n) (%)	Cases diagnosed by Dr. B (n) (%)	Cases diagnosed by Dr. A (n) (%)	Cases diagnosed by Dr. B (n) (%)
1	Kidney 30 (75.0%)	Kidney 38 (95.0%)	Bladder 14 (45.2%)	Stomach 11 (35.5%)
2	Spleen 26 (65.0%)	Liver 26 (65.0%)	Stomach 10 (32.3%)	Large Intestine 10 (32.3%)
3	Liver 25 (62.5%)	Spleen 17 (42.5%)	Large Intestine 9 (29.0%)	Gallbladder 10 (32.3%)
4	Lung 12 (30.0%)	Heart 14 (35.0%)	Gallbladder 8 (25.8%)	Bladder 8 (25.8%)
5	Heart 0 (0.0%)	Lung 9 (22.5%)	Triple Energiser 0	Triple Energiser 5 (16.1%)
6	Pericardium 0	Pericardium 0	Small Intestine 0	Small Intestine 1 (3.2%)

Key: n = number

Table 9.8 Agreement on the three most commonly diagnosed Zang and Fu Organs involved

Zang Organs	Valid cases (n)	Cases diagnosed by Dr. A (n)	Cases diagnosed by Dr. B (n)	Agreed cases (n)	Agreement (%) §
Kidney	40	30	38	28	70.0
Liver	40	25	26	17	42.5
Spleen	40	26	17	14	35.0
Fu Organs	Valid cases (n)	Cases diagnosed by Dr. A (n)	Cases diagnosed by Dr. B (n)	Agreed cases (n)	Agreement (%) §
Bladder	31	14	8	4	12.9
Stomach	31	10	11	6	19.4
Large Intestine	31	9	10	4	12.9
Gallbladder	31	8	10	5	16.1

Key: n = number; § - partial agreement criteria

9.6.3.2 Meridian involvement

The mean number of involved Meridians was the same for the two practitioners, an average of two Meridians. The level of agreement on the actual Meridians involved using a strict agreement criterion was 15.0%%, whereas it was 75.0% using the partial agreement criterion.

As for the most commonly involved Meridians, Practitioner A diagnosed 55.0% of cases as involving the Kidney Meridian, 50.0% the Liver Meridian, 42.5% the Spleen Meridian and 25.0% the Stomach Meridian. Practitioner B had a similar rank order for the first two meridians: Kidney Meridian (56.4%) and Liver Meridian (42.5%) with the order reversed for the Spleen Meridian (22.5%) and Stomach Meridian.

Agreement on the individual Meridians was low. It was 30.0% for the Kidney Meridian, 25.0% for the Liver Meridian, 15.0% for the Spleen Meridian and 2.5% for the Stomach Meridian.

See Table 9.6, Table 9.9 and Table 9.10 for more details.

Table 9.9 Rank of most commonly diagnosed single Meridians

Rank	Meridian	
	Cases diagnosed by Dr. A (n) (%)	Cases diagnosed by Dr. B (n) (%)
1	Kidney Meridian 22 (55.0%)	Kidney Meridian 24 (56.4%)
2	Liver Meridian 20 (50.0 %)	Liver Meridian 17 (42.5 %)
3	Spleen Meridian 17 (42.5 %)	Stomach Meridian 12 (30.0 %)
4	Stomach Meridian 10 (25.0 %)	Spleen Meridian 9 (22.5 %)
5	Gallbladder Meridian 6 (15.0 %)	Gallbladder Meridian 8 (20.0 %)
6	Bladder Meridian 5 (12.5 %)	Bladder Meridian 8 (20.0 %)

Table 9.10 Agreement on the most common single Meridians

Meridian	Valid cases (n)	Cases diagnosed by Dr. A (n)	Cases diagnosed by Dr. B (n)	Agreed cases (n)	Agreement (%)§
Kidney Meridian	40	22	24	12	30.0
Liver Meridian	40	20	17	10	25.0
Spleen Meridian	40	17	9	6	15.0
Stomach Meridian	40	10	12	1	2.5

Key: n = number; § - partial agreement criteria

9.6.3.3 CM Syndrome Diagnosis

The average number of CM Syndromes diagnosed by Practitioner A was 2.0, while it was 2.9 for Practitioner B. There was no strict agreement between the two practitioners on CM Syndrome Diagnosis based on a strict match on single CM Syndromes. When it was assessed by partial agreement, level of agreement was 50.0%.

The most frequently diagnosed CM Syndromes by Practitioner A were Spleen Qi Deficiency (53.8%), Liver Blood Deficiency (33.3%) and Kidney Qi Deficiency (33.3%). The most frequently diagnosed Syndromes for Practitioner B were Kidney Yin Deficiency (56.4%), Liver Yin Deficiency (41.0%) and Kidney Qi Deficiency (29.1%). Results are set out in Table 9.11.

Level of agreement was calculated for these six most commonly diagnosed CM Syndromes. Results are set out in Table 9.12. Level of agreement on CM Syndrome diagnosis was also low. The highest agreement on a single Syndrome was for Spleen Qi Deficiency (23.1%), followed by Kidney Yin Deficiency (12.8%). For other Syndromes, agreement was very low.

Table 9.11 Ranking of most commonly diagnosed single CM Syndromes

Rank	Syndrome Diagnosis	
	Cases diagnosed by Dr. A (n) (%)	Cases diagnosed by Dr. B (n) (%)
1	Spleen Qi Deficiency 21 (53.8%)	Kidney Yin Deficiency 22 (56.4%)
2	Liver Blood Deficiency 13 (33.3%)	Liver Yin Deficiency 16 (41.0%)
3	Kidney Qi Deficiency 13 (33.3%)	Kidney Qi Deficiency 9 (23.1%)
4	Liver Qi Stagnation 6 (15.4%)	Spleen Qi Deficiency 9 (23.1%)
5	Liver Yin Deficiency 5 (12.8%)	Kidney Yang Deficiency 7 (17.9%)
6	Kidney Yin Deficiency 5 (12.8%)	Liver Qi Stagnation 5 (12.8%)

Key: n = number

Table 9.12 Agreement on the most common single CM Syndrome Diagnosis

Syndrome	Valid cases (n)	Cases diagnosed by Dr. A (n)	Cases diagnosed by Dr. B (n)	Agreed cases (n)	Agreement (%) §
Spleen Qi Deficiency	39	21	9	9	23.1
Kidney Yin Deficiency	39	5	22	5	12.8
Liver Blood Deficiency	39	13	4	1	2.6
Liver Yin Deficiency	39	5	16	3	7.7
Kidney Qi Deficiency	39	13	9	2	5.1

Key: n = number; § - partial agreement criteria

9.6.3.4 Ranking of four diagnostic methods

The practitioners also ranked which the symptoms or signs were most important in leading them to their diagnosis. For Practitioner A, symptoms were the most important evidence upon which to make their diagnosis with evidence from the Inquiry part of the CM examination ranked as most important in 95% of cases (general symptoms in 65.0% cases and specific knee symptoms in 30.0%). For Practitioner B, tongue diagnosis (one of the Inspection techniques) was regarded as the most important method leading to the final Syndrome Diagnosis.

In general, Pulse diagnosis (Palpation) was not considered very important by either practitioner in the process of making a CM Syndrome Diagnosis. None of the practitioners used information from Auscultation as diagnostic evidence for knee OA.

See Table 9.13 for more details.

Table 9.13 Rank of the importance of symptoms / signs in the Syndrome diagnosis

	Dr.	Valid cases (n)	General Symptoms: n (% cases)	Knee Symptoms: n (% cases)	Tongue: n (% cases)	Pulse: n (% cases)	Auscultation: n (% cases)
Rank1	A	40	26 (65.0%)	12 (30.0%)	2 (5.0%)	1 (2.5%)	0 (0.0%)
	B	40	13 (32.5%)	0 (0.0%)	18 (45.0%)	9 (22.5%)	0 (0.0%)
Rank2	A	40	29 (72.5%)	7 (17.5%)	3 (7.5%)	1 (2.5%)	0 (0.0%)
	B	40	28 (70.0%)	0 (0.0%)	8 (20.0%)	4 (10.0%)	0 (0.0%)
Rank3	A	35	24 (68.6%)	3 (8.6%)	6 (17.1%)	2 (5.7%)	0 (0.0%)
	B	40	29 (72.5%)	2 (5.0%)	4 (10.0%)	5 (12.5%)	0 (0.0%)
Rank4	A	24	5 (20.8%)	5 (20.8%)	11 (45.8%)	6 (25.0%)	0 (0.0%)
	B	36	26 (72.2%)	3 (8.3%)	2 (5.6%)	5 (13.9%)	0 (0.0%)

Key: n = number

9.7 Discussion

9.7.1 Reproducibility of clinical diagnostic variables

9.7.1.1 Reproducibility of Inquiry variables

CM diagnosis seldom relies on laboratory tests unlike western medicine.(Knottnerus et al., 2002) Inquiry in CM usually involves many subjective questions and answers which may seem less reliable in term of reproducibility. However, Inquiry has become central to the art of CM diagnosis, not only because we need information from a patient's real experience of their illness, but also because it is an interactive process which can influence the treatment results and reflects the underlying physical, emotional and mental condition of the patient.(Maciocia, 2004) There are many different ways of eliciting such information from patients. The CM Assessment form used in this study, based on one developed by O'Brien and colleagues (O'Brien et al., 2009a, O'Brien et al., 2009b) attempted to standardise the Inquiry process. The validity of this is discussed in the Methods Chapter.

In this study, a relatively good level of agreement for most Inquiry variables was found. For almost 50% of the Inquiry endpoints there was a 'substantial' to 'almost perfect' level of agreement. These endpoints with a high level of agreement cover the areas of ten traditional or 'rhythmic' questions that characterise CM diagnosis.(Deng et al., 1984) These questions mainly asked about the presence or absence of a certain symptom, a yes/no answer, which makes it relatively easy to achieve agreement between different raters.

For approximately 20 of the Inquiry variables (16 questions), there was a 'moderate' to 'fair' level of agreement. However the limitations of the Kappa statistics need to be considered. Firstly, there were some questions with a 'fair' level of agreement such as characteristics of abdominal pain that only had a small numbers of valid cases for Kappa analysis, providing insufficient data from which to judge if those variables were reliable or not. Secondly, in the case of some variables where the Kappa coefficient interpretation indicated only 'moderate' to 'fair' levels of agreement, the actual percentage agreement may have been quite high. However because the number of responses in the Kappa tabulation cells was unequal or skewed (if one practitioner chose one response most of the time, for example), then the Kappa coefficient was comparatively low- this is a limitation of the Kappa statistics. (Bryington et al., 2002) For instance, the question of 'presence of body pain' and 'level of appetite' both had 95.0 overall precent agreement, but κ was 0.48. A similar result can be found in the question of 'presence of incomplete sensation of urination', where the Kappa coefficient was low indicating poor agreement (κ = -0.06), even though the percentage agreement was 87.5%. It is important to remember in interpreting the level of agreement, however, that the Kappa coefficient is a measure of the level of agreement beyond that expected by chance. The percentage agreement on its own may be misleading. There were also 23 questions which could not be analysed by Kappa coefficient. Reasons included missing data for Kappa tabulation cells, or small number of valid cases for a particular question. For example, one practitioner noted that none of the participants had fever while the other practitioner recorded one case of 'presence of fever'.

Given the practitioners were using a fixed form of words in this study and choices of responses were fixed, it is not surprising that there was a reasonably high level of agreement on Inquiry variables. This contrasts with clinical practice in which asking an open-ended question may elicit more varied responses. Other research has found the use of objective questionnaires instead of traditional case notes for Inquiry can increase agreement on CM diagnosis between practitioners for rheumatoid arthritis, (Zhang et al., 2008a) and improve the reliability of the diagnosis of the Syndrome of Yin Deficiency amongst college students and office workers.(Lee et al., 2007)

9.7.1.2 Reproducibility of Inspection variables

Inspection in CM is based on the concept of correspondence between the Internal Organs and their external manifestations. Eight aspects of the body were used as Inspection variables, including appearance of the tongue, although more exist. Others such as appearance of the eyes, nose, ears and chest were not utilised as they do not add value with respect to diagnosis of knee OA.

In general, a 'slight' to 'fair' level of agreement was found for the majority of Inspection variables. There were only two variables which had 'moderate' agreement between two practitioners: observation of the amount of hair and the type of body frame. Only one question, the temperature of hands, achieved 'substantial' agreement ($\kappa = 0.66$). Given the form used fixed response choices, the findings indicate a relatively low level of agreement overall for Inspection variables.

The results are similar to those found in O'Brien and colleagues' study that found variable levels of agreement for Inspection endpoints, with most endpoints achieving a level of agreement between all three practitioners as either 'slight' or 'fair'.(O'Brien et al., 2009b) However in their study, when level of agreement between at least two practitioners was calculated, there was 'almost perfect' agreement for five out of 14 inspection variables and 'substantial' agreement for two Inspection variables.(O'Brien et al., 2009b)

The reasons for relatively low levels of agreement in this study may include differences in practitioner training. In this current study, one practitioner was trained in China (in

Chinese) while another learned CM in Australia (in English). There might be some subtle differences in the understanding of CM concepts and differences in personal experience that could have influenced results. For example, the colour of complexion is affected by racial group, and discrimination of the paleness of a Caucasian patient may be different than in an Asian patient. In this study, one practitioner diagnosed all participants as having a 'normal' complexion colour while the other thought there were some patients with 'abnormal' colours, which led to 72.5% agreement. The level of agreement of the colour of complexion in O'Brien and colleagues' study was 93% between at least two practitioners (Kappa 0.85, 'almost perfect' agreement), but only 31% (Kappa 0.28) between all three practitioners. Another reason for low levels of agreement on Inspection variables may be slight differences in lighting between consultation rooms used by the two practitioners.

Although tongue diagnosis is an important part of CM, supporting evidence of its reliability was not forthcoming in this study. Only a 'fair' level of agreement was found for the presence of teeth marks on the tongue, the presence of red tip on the tongue, the presence of cracks on the tongue, the thickness of the tongue coating, and the colour of the tongue coating. Only a 'slight' level of agreement was found for colour of the tongue body. A similar finding was also reported by Kim and colleagues, (Kim et al., 2008) although they used slides of tongues for their study.

The low agreement on Inspection variables found in this study suggests that these aspects of the CM examination are quite subjective, and that clear definitions of those characteristics in CM are needed. Work is already underway in China to develop more objective methods for tongue diagnosis, like colour detection instruments and computerised image analysis systems based on the red/green/blue (RGB) model, the 'Lab' model (a colour-opponent space model with three dimensions, dimension L for lightness and dimensions 'A' and 'B' designating the colour-opponent dimensions), the YUV model (Y designating the luminosity or brightness component and U and V the chromaticity or colour components), and the HSL (hue/saturation/lightness) model.(Chen and Zhang, 2008, Wang et al., 2005, Wei et al., 2002, Weng and Huang, 2001)

Studies in western medicine have also indicated considerable variation between observers in physical examination.(Joshua et al., 2005, Gjłrup et al., 1984, Vogel, 1992, Hansen et al., 1994, Shinar et al., 1985)

9.7.1.3 Reproducibility of Auscultation variables

Although auscultation is not a major part of diagnosis process in CM, it is still necessary to test its reliability as a diagnostic method. The level of agreement between two practitioners on the strength of voice and character of breathing sounds was reasonably high, 82.5% and 97.5% respectively, though Kappa was unable to be calculated. This result is similar to the findings in O'Brien and colleagues' study which showed 'almost perfect' agreement between at least two practitioners, though their findings were lower for agreement between all three practitioners (60% and 69% agreement for voice strength and character of breathing sounds, respectively).(O'Brien et al., 2009b) A literature review of western medicine examination (Joshua et al., 2005) indicated 'fair' agreement on some signs in a respiratory examinations, such as breath sound intensity, bronchial breath sounds, crackles sound, cough and tachypnoea ($0.21 \leq \kappa \leq 0.40$). More studies are needed to establish the reproducibility of auscultation variables in CM.

9.7.1.4 Reproducibility of Palpation variables

Palpation in CM includes palpation of pulse, chest and abdomen, as well as Meridians and acupoints. But the most important part of palpation in real practice is pulse diagnosis. The results of this study indicated 'poor' agreement for one aspect of pulse diagnosis, 'slight' agreement for four aspects, and 'fair' for one aspect. The results support the notion that pulse diagnosis is the most difficult part of the art of CM diagnosis, which requires extensive clinical experience to master.(Maciocia, 2004)

O'Brien and colleagues' study found a 'substantial' level of agreement between two practitioners on pulse speed, a 'fair' level of agreement between all three practitioners on pulse force, and 'slight' agreement between all three practitioners on pulse location.(O'Brien et al., 2009b) Agreement of the pulse force and location increased dramatically to 'almost perfect' when compared between at least two practitioners.(O'Brien et al., 2009b) A review of reliability studies of pulse diagnosis

(O'Brien and Birch, 2009) showed that the agreement could vary from a low level to very good agreement. However, care should be taken in making comparisons across studies.

9.7.2 Reproducibility of the diagnosis of the Eight Guiding Principles

The identification of Syndromes according to the Eight Guiding Principles is the foundation for all the other methods of Syndrome Differentiation, allowing the CM practitioner to identify the location and nature of the disharmony and establish the principle of treatment. There is no condition that is too complex to fall outside the scope of the diagnosis of the Eight Guiding Principles.(Maciocia, 2004)

The results from this study showed agreement on the Interior/Exterior pair was 97.5%. There was only one patient amongst 40 OA patients who was diagnosed as having the pattern of Half-Interior and Half-Exterior by one practitioner and the others were all identified as 'Deficiency' patterns. This is consistent with CM theory that suggests that knee OA mainly is caused by Deficiency of Yin, Yang, Qi and Blood (the vital essences). It also corresponds with the CM view on OA, which is that the root of the disease is a weakness of the person's constitution (see Chapter 5).

Kappa values for the Hot/Cold pair (32.5% agreement, $\kappa = 0.08$) and Excess/Deficiency pair (77.5% agreement, $\kappa = -0.05$) indicated there were 'slight' and 'poor' agreement between two practitioners. This finding was similar to O'Brien and colleagues' study on the reliability of diagnosis according to the Eight Guiding Principles, which also found that the level of agreement was 'slight' for nature of disorder (Excess/Deficiency) and for the temperature characteristics (Hot/Cold) between all three practitioners for patients with hypercholesterolemia, though agreement was higher when compared between at least two practitioners.(O'Brien et al., 2009a)

Low agreement on Hot/Cold principles for OA patients may indicate that this is a less reliable tool for OA diagnosis. The Hot/Cold pair may be more useful for other diseases. In other words, the Eight Guiding Principles may not necessarily be useful characteristics in every condition or disease. For example, soft tissue injury is a case in point as it does not involve any Hot or Cold symptoms. Hypercholesterolemia and OA might be the case too. In addition, low agreement on Excess/Deficiency Principles ($\kappa = -0.05$) may simply

reflect the complex pathogenesis of OA in CM which is treated as a Syndrome with a deficient root (‘ben’) and excessive or ‘full’ branch (‘biao’ or symptoms). At some stages of the disease, OA of the knees may manifest different or mixed symptoms and signs.

The Yin/Yang pair is generally a summary of the other six Principles. Yin represents Interior, Deficiency and Cold, while Yang represents Exterior, Excess and Heat. One practitioner categorised all participants as Yin, and the other practitioner rated 27 participants (67.5% of all participants) as Yin. The majority of participants were diagnosed as having an ‘Interior’ condition. There was 77% agreement on the ‘Deficiency/Excess’ pair with the majority being ‘Deficiency’ (39 participants diagnosed as Deficiency amongst 40 patients by Practitioner A and 32 patients diagnosed with Deficiency by Practitioner B), though the Kappa value indicated a poor level of agreement. These results lend some support to the argument that OA of knee is more likely to be an internal disease with the manifestations of deficient symptoms (such as the weakness of knee, impaired movements and pain or stiffness in the knees), that is, some ‘empirical’ evidence to support the notion of pathogenesis of OA according to CM theories. Caution in interpreting the results needs to be taken since the Kappa coefficient could not be calculated for two of the pairs.

We cannot simply draw a conclusion from this one OA study that the Eight Guiding Principles are unreliable tools for CM diagnosis, especially for guiding Syndrome Diagnosis. A study of the inter-rater reliability of CM diagnosis of chronic low back pain (Hogeboom et al., 2001) found that the Eight Guiding Principles were not equally important for all acupuncturists. To establish if it is or is not a reliable diagnostic tool, more studies should be conducted in different clinical conditions.

9.7.3 Reproducibility of CM Syndrome diagnosis based on Zang Fu theory

Like other studies, such as those conducted in low back pain (Birch and Sherman, 1999, Hogeboom et al., 2001), irritable bowel syndrome (Sung et al., 2004), headaches (Coeytaux et al., 2006), rheumatoid arthritis (Zhang et al., 2005a) and hypercholesterolemia (O'Brien et al., 2009a), a low level of agreement on CM Syndrome diagnosis was also found in this study for OA of the knee. Although the average numbers

of CM Syndromes diagnosed for the two practitioners were 2.0 and 2.9 respectively, the level of strict agreement was 0% and partial agreement was only 50.0%.

In this study, we adopted an open-ended CM Syndrome diagnosis in order to investigate the potential spectrum of possible OA Syndromes and also follow the normal diagnostic process in real practice. Therefore, this design is more likely to result in a lower level of agreement than if a fixed list of Syndromes was provided. The term 'osteoarthritis' is still a relatively new disease name in CM books and there is no generally accepted Syndromes list for OA yet. The most common single Syndromes were Spleen Qi Deficiency, Kidney Yin Deficiency, Liver Blood Deficiency, Liver Yin Deficiency, Kidney Qi Deficiency and Liver Qi Stagnation. However, the highest agreement on these single Syndromes was Spleen Qi Deficiency (23.1%), followed by Kidney Yin Deficiency (12.8%). We can see the difference easily between the findings in this study and those reported in the literature which lists other CM Syndromes such as 'Deficiency of Kidney Essence', 'Cold blockage with Deficiency of Yang', 'Blood stagnation', 'Syndrome of Damp and Heat accumulation', 'Syndrome of Phlegm blockage', 'Syndrome of Deficiency of Liver Blood' and 'Wei Syndrome'.(Xiao, 2004, Qu and Xiao, 2008, Xiao and Zheng, 2003, Cao et al., 2006b, Min et al., 2003) We cannot claim that the majority OA patients have Spleen Qi Deficiency or Kidney Yin Deficiency based on the results of this one study- after all, this study was not an epidemiological survey which would need a much larger numbers of participants.

However, the results do lend some support to the theoretical basis of OA described in Chapter 5. According to theory, OA is due to a Deficiency of the Kidney and Liver, especially relating to Essence and Blood. CM holds that the 'Liver and Kidney have a common source' (Maciocia, 2005) that Liver Blood nourishes Kidney Essence and that the Kidney in turn contributes to making Blood. Furthermore, the Spleen makes Blood and the Liver stores Blood. Therefore, the Kidney, Liver and Spleen have a very close relationship in the development of OA, according to theory. This relationship was also reflected in the results of this reliability study. In this study, the top three ranking involved Zang Organs for two practitioners were Kidney (70.0% agreement), Liver (42.5% agreement) and Spleen (35.0% agreement). Although the average numbers of

involved Zang Organs for the two practitioners were 2.4 and 2.6 respectively, partial agreement of involved Zang Organs was 95.0%. Thus, our study suggested there was high agreement of involved Zang Organs in Syndrome diagnosis for knee OA, but low agreement in general single CM Syndrome diagnosis for knee OA.

In addition, although agreement about the involved Meridians was low, both practitioners generally agreed the most commonly involved Meridians were the Kidney Meridian (30.0% agreement), Liver Meridian (25.0% agreement) and Spleen Meridian (15.0% agreement), all belonging to the category of Yin Meridians.

There were many reasons which could contribute to the low agreement and various Syndrome diagnoses of knee OA, such as different clinical training and experience between practitioners, the study population (Caucasian only), or the stage of OA (knee OA with the severity of Grade II or III). Since it is common in CM that many diseases can share several common CM syndromes or a disease can also have several different Syndromes, the development of a Syndrome Diagnosis tool to standardise CM diagnosis is not easy, though some assessment forms and questionnaires have been developed in order to standardise and clarify CM terms and collect clinical data.(Lee et al., 2007, Mist et al., 2009, Schnyer et al., 2005, O'Brien et al., 2009a)

The reliability of CM Syndrome diagnosis may be improved through training processes.(Zhang et al., 2008a, Schnyer et al., 2005, Mist et al., 2009) MacPherson and colleagues (MacPherson et al., 2004) reported that diagnostic concordance of low back pain amongst five practitioners had become reasonable (47-75% for primary syndromes and 56-80% for secondary syndromes) on the basis of a series of meetings prior to the study, in which they shared their personal experience to develop the Syndromes shortlist and standardise the definitions of the Syndromes. However in their study, the Syndrome diagnosis was made by practitioners choosing from three pre-defined Syndromes rather than an open-ended diagnosis process. (MacPherson et al., 2004) Zhang and colleagues (Zhang et al., 2008a) and Sung and colleagues (Sung et al., 2004) also demonstrated that a training exercise to obtain consensus on CM diagnostic criteria can lead to a higher agreement on CM diagnosis. This could explain the lower levels of agreement of

Syndrome Diagnosis in this study and other studies (O'Brien et al., 2009a) where there was no discussion between practitioners nor prior training.

We also investigated the emphasis placed on diagnostic techniques or information which led to a final diagnosis. Although the integration of information from all four diagnostic methods has always been a principle of CM diagnosis,(Deng et al., 1984) there is likely to be considerable variation between practitioners in terms of emphasis of particular techniques for making a diagnosis. O'Brien and colleagues found that pulse and tongue diagnosis were the most commonly used techniques leading to a CM Syndrome diagnosis in hypercholesterolemia patients.(O'Brien et al., 2009a) However in our study in OA patients, Inquiry (symptoms) was found to be more important to the practitioners in arriving at a Syndrome diagnosis. Practitioner A listed symptoms as the first important evidence to make a diagnosis for 95.0% cases, including general symptoms (65.0% cases) and knee symptoms (30.0% cases). Practitioner B ranked Inspection (tongue diagnosis) as the most common technique for making a diagnosis (45.0% cases), and ranked Inquiry (symptoms) as the second-most important piece of diagnostic evidence. The different findings from the two studies may indicate that the weighting of diagnostic information may change for particular diseases, or it may simply reflect the different emphasis of the individual practitioners. More studies need to be done in order to clarify this issue.

9.8 Features and limitations of the study

There were a number of factors that have emerged, upon reflection, which may have potentially affected the results of this reliability study. Firstly, the use of the CM assessment form used for data collection is probably not reflective of real clinical practice, in which the consultation usually starts with inquiry about the patient's main complaint. Most of the ensuing questions, inspection, palpation and auscultation then focus on the main complaint in order to find out the links between different symptoms and signs, and then extract the key points, thus arriving at the Syndrome Diagnosis. The use of a CM assessment form could serve to interrupt or sidetrack the more realistic clinical thinking process by requiring the practitioner to ask about symptoms/signs that are not necessarily relevant. It may be likened to breaking a holistic picture into too many (diagnostic) pieces. On reflection, some of the questions with respect to the knee were more general in nature

and may not have been specific enough for the condition of OA. For example, some patients reported that they did not have pain or stiffness, but had 'discomfort'. This is a limitation of using fixed categorical variables.

Secondly, the difference in CM training and experience between the two practitioners may have contributed to the variability in observations and diagnosis. Some signs are open to interpretation and that interpretation will likely be influenced by the clinical training and experience of the practitioner. For example, a red tip of the tongue may be interpreted as a sign of Yin deficiency or excess Heat in the Lung or Heart. It is believed that agreement is likely to be underestimated when there are those differences between practitioners.(Crewson, 2005) For example, Practitioner B diagnosed Kidney Yin deficiency in 22 cases and of these, about one third were noted to have a red tip of the tongue. In contrast, Practitioner A diagnosed 6 cases of Yin deficiency and in only one of these a red tip of the tongue was noted. This suggests that Practitioner B used presence of a red tongue tip as evidence to support the diagnosis of Yin deficiency. A similar situation also could be found in the weighting of diagnostic methods. Practitioner B reported tongue inspection as the most important evidence used to diagnose (45.0% participants), but Practitioner A only reported this technique as valuable for 5.0% of participants. Based on the prior clinical experience and training of a practitioner, a practitioner may have a pre-conceived notion of the diagnosis that may influence their observations and the interpretation of that data.

Thirdly, there was no fixed list of Syndromes of knee OA used in this study, which is likely to reduce the potential level of agreement between practitioners. Studies have shown that the reliability of CM diagnosis achieved reasonable agreement when pre-defined Syndromes were used.(MacPherson et al., 2004, Zhang et al., 2008a) However, there is no a generally accepted Syndromes list of knee OA, so we adopted the approach of using an open-ended Syndrome Diagnosis. Also, this mirrors real clinical practice.

Fourth, there was no training prior to the study. Studies indicate that prior training influenced level of agreement positively. Zhang and colleagues found the average agreement of CM diagnosis in rheumatoid arthritis amongst three practitioners was 28.2% (Zhang et al., 2004b) and increased to 73 % in a repeat study after a training

session. (Zhang et al., 2008a) It would be interesting to conduct further research and investigate if prior training improves reliability of diagnosis in knee OA.

Finally, the limitations of the Kappa coefficient might not effectively elucidate the real level of agreement. Although the Kappa coefficient is thought to be the preferred statistical method for calculating the degree and significance to nominal categories,(Langenbucher et al., 1996) when there is a large proportion of agreement and most of that agreement is limited to only one of the possible rating choice, Kappa becomes unstable or even inappropriate as a statistic.(Haas, 1991) This kind of occurrence was not unusual in this study. For example, the percent agreement for the question, 'presence of tongue coating' was 90.0%. There was only one participant reported as 'no' (amongst 40 participants) by Practitioner B and only two cases reported as 'no' by Practitioner A. Thus the data in the 2 × 2 table used to calculate Kappa is skewed or unbalanced. The Kappa was -0.04, indicating 'poor' agreement, despite the very high percent agreement. Therefore, care needs to be taken in interpreting the Kappa results in this situation.

9.9 Conclusion

This study investigated the reliability of the CM diagnostic process in a comprehensive and systematic way, investigating the Four Diagnostic Methods, Syndrome Diagnosis according to the Eight Guiding Principles, and Syndrome Diagnosis according to the Zang Fu theory. There was variation in the level of agreement between two practitioners on clinical information collected from the Four Diagnostic Methods of a CM examination: inquiry, inspection, auscultation and palpation. There was a relatively good level of agreement for Inquiry and Auscultation variables, and in general a low level of agreement for Inspection and Palpation variables.

Considering the nature and characteristics of knee OA, a satisfactory level of agreement was found on the diagnosis of Interior/Exterior and Yin/Yang pairs according to the Eight Guiding Principles, but poor agreement for Hot/Cold and Excess/Deficiency. Results support the notion that knee OA is more likely a disease with characteristics of Interior, Deficiency and Yin.

Agreement on the CM Syndrome Diagnosis between two practitioners was low based on an open-ended Syndrome diagnosis, although the main involved Zang Organs were broadly agreed on, being Kidney, Liver and Spleen. The results did not demonstrate clearly agreed on CM Syndromes of knee OA. Larger scale studies will be required for this purpose. In addition, no CM diagnostic endpoints were demonstrated to be sufficiently consistent to justify inclusion in the clinical efficacy trial that was the subject of this thesis.

Chapter 10 Results of the Randomised Controlled Trial into the Efficacy of the Bai Niu Capsule in treating symptoms of knee OA

10.1 Introduction

Although Chinese herbal medicine (CHM) has been commonly used in China for the treatment of patients with OA of the knee, there are few rigorous studies of the efficacy and safety of CHM in the treatment of OA to date. This study was the first randomised, double-blind, and placebo-controlled clinical trial of a CHM formula (the Bai Niu capsule) in an Australian OA population. This project intended to improve the quality of evidence in this domain by conducting a rigorous study using established best practice research protocols. In addition, a new trend in the Chinese medicine (CM) clinical treatment of OA, that OA is a combined disease of Bi Syndrome and Wei Syndrome has been applied in the study in order to provide clinical evidence and contribute to the development of CM theory.

10.2 Study objectives

10.2.1 Primary

1. To evaluate the efficacy of a CHM formula, the Bai Niu Capsule, designed to address both Bi Syndrome and Wei Syndrome, in alleviating symptoms of OA of the knee compared to placebo as measured by changes in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) - Visual Analogue Scale format (VAS) from baseline to 12 weeks post randomisation, and at 1 month following the completion of treatment (Week 16).

2. To assess the safety and tolerability of the CHM formula over 12 weeks as determined by biochemical and metabolic tests and the incidence of any side effects.

10.2.2 Secondary

1. To assess the efficacy of the Bai Niu Caspsule compared with placebo in altering general wellbeing over 12 weeks treatment and 4 weeks following the completion of the treatment, as measured with the Short Form Health Survey (SF-36).

2. To assess the effects of the Bai Niu Capsule compared with placebo over 12 weeks and 4 weeks following completion of treatment by measuring changes in the Patient Global Assessment.

3. To assess the effects of the Bai Niu Capsule compared to placebo over 12 weeks by measuring changes in the Physician Global Assessment.

10.3 Hypotheses

The study had the following null hypotheses:

1. There will be no change of WOMAC index, SF-36, Patient Global Assessment from baseline at 12 weeks post- randomisation, and at one month following the completion of treatment (Week 16) in the Bai Niu group or placebo group.

2. There will be no change of Physican Global Assessment from baseline at 12 weeks post randomisation in the Bai Niu group or placebo group.

10.4 Materials and methods

This was a randomised, double-blind, placebo-controlled parallel group study designed to examine the efficacy of the CHM formula, the Bai Niu Capsule, in alleviating symptoms of OA of the knee over 12 weeks. For a more detailed description of the methods used, refer to Chapter 7.

10.4.1 Study participants

10.4.1.1 Inclusion and exclusion criteria

The inclusion criteria were:

1. Unilateral or bilateral OA of the knee fulfilling the criteria provided the American College of Rheumatology (ACR) 1995 (Hochberg et al., 1995) were eligible to participate. The ACR criteria were: knee pain and radiographic osteophytes, and at least one of the following three items:

    1) age $>$ 50 years;

2) morning stiffness ≤ 30 minutes in duration; and

3) crepitus on motion

2. Radiographic evidence of OA was based on the ranking score of the Kellgren-Lawrence radiographic system (Kellgren and Lawrence, 1957). The primary tibio-femoral OA either grade II or grade III severity was considered as a condition of inclusion.

3. Participants were fluent in the English language or able to give informed consent and complete study assessments with the assistance of an interpreter.

4. Participants provided written informed consent to participate in the study and were willing to comply with the study procedures.

5. No abnormal finding of clinical relevance at the screening evaluation.

The exclusion criteria were:

1. Accompanying OA of hip of sufficient severity to interfere with the functional assessment of the knee.

2. Secondary OA or rheumatoid inflammatory or any other type of arthritis.

3. Previous and ongoing treatment with oral symptomatic slow acting drugs in OA treatment within 2 months before the study (e.g. glucosamine sulphate, chondroitin sulphate, diacerein, piascledine).

4. Requiring arthroplasty within 2 months or anticipating any need for a surgical procedure on the involved joint during the study.

5. Have received intra-articular treatment of the involved joint or joint lavage in the previous 6 months (e.g., corticosteroids or hyaluronic acid).

6. Knee surgery during the previous 3 months.

7. Hypersensitivity to NSAIDs.

8. Taking any regular prescribed medicine for OA during the trial except for pain medications that were taken ‘as required’ for break-through pain.

9. Any significant systemic illnesses or medical conditions that could lead to difficulty complying with the protocol.

10. Screening or baseline liver function tests aspartate transaminase (AST) and/or alanine transaminase (ALT) >2.5 times the upper limits of laboratory reference range.

11. Any additional condition(s) that, in the investigator’s opinion, would prohibit the subject from completing the study, or not be in the best interest of the subject.

12. Pregnancy or active breast-feeding. Female subjects of childbearing potential (not postmenopausal for at least one year or surgically sterilised) agreed not to become pregnant during the duration of the study and male subjects agreed not father kids. Specifically, they agreed to use an appropriate contraceptive regimen.

13. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel, electrolytes including Na^+ and K^+, and urinalysis).

14. Evidence of clinically relevant, cardiovascular, haematological, gastrointestinal, hepatic, renal, endocrine, pulmonary, neurologic or psychiatric disorder.

15. Use of any over the counter product medications, herbal products, diet aids, hormone supplements, etc., within 14 days prior to dosing unless approved by the Principal Investigator.

16. Have participated in a clinical trial or receipt of an experimental therapy within 30 days prior to inclusion.

17. Unwilling or unable to provide written informed consent.

The radiographic assessment was conducted by a radiologist from the Alfred Hospital, Melbourne, Australia. The medical assessments and physical examination were conducted by a rheumatologist from the Alfred Hospital.

10.4.1.2 Participant recruitment

The study was conducted in the Alfred Hospital in conjunction with the Centre for Clinical Trials, Nucleus Network, Australia. Ethics approval was granted by the Alfred Hospital Human Research Ethics Committee (HREC) and Victoria University (HREC). Participants were recruited through newspaper advertisements. Participants were posted a Participant Explanatory Statement prior to attending a screening visit and provided with a written informed consent form prior to enrolment in the study. All participants gave consent to participate.

Participants were all assigned to the treatment or placebo group in accordance with the randomisation code in a sequential manner. Randomised participants who did not complete the study were recorded as drop-out cases.

10.4.2 Herbal preparation and dispensing

The herbal medicine and placebo were manufactured as soft gelatin capsules by a Taiwanese company has Australian Good Manufacturing Practice (GMP) certification. Each capsule of the Chinese herbal medicine formula contained concentrated herbal granules. The placebo capsules were filled with lactose of United States Pharmacopeia (USP) grade for pharmaceutical use.

The study medications were stored at the clinical trial pharmacy of the Alfred hospital in accordance with regulatory requirements. Only authorised pharmacy staff could supply the study medications. Eligible participants were dispensed six bottles of herbal medicine or placbeo capsules (12 weeks dosage) at the randomisation visit (visit 2). The dose of the study medication was five capsules three times a day (morning, middle of the day and evening), half an hour after food, thus totalling 15 capsules.

10.4.3 Randomisation and Blinding

A block randomisation number code was generated by computer overseen by a biostatistician. A copy of the randomisation code was held by the candidate’s principal supervisor to be opened in case of an adverse event. Study participants were administered study medications sequentially in order of participation in the study. Study medications

were administered in labelled bottles. Labelling of the bottles was conducted by an external pharmaceutical storage company in South Australia, which was not involved in the distribution of medication to study participants. As there were no severe adverse effects, the randomisation code was only revealed after the statistical analyses were completed.

10.4.4 Study Procedure

Each subject attended a total of six clinic visits including the screening visit (visit 1), the baseline/randomisation visit (visit 2/week 0), three visits during the treatment period (visit 3/week 2, visit 4/week 6, and visit 5/week 12), and the follow-up visit after cessation of the medication (visit 6/week 16).

At the screening visit, demographic data, vital signs, blood and urine tests and a comprehensive physical examination (including 12-lead electrocardiography and knee X-ray), medical history, and concomitant medications were recorded. Participants were asked to provide a complete list of prescription and over-the-counter medications that have been taken within four weeks prior to the screening visit. The investigators were also kept informed about any new medications taken during the course of the study. All concomitant medications taken during the study were documented with indication, dose information, and dates of administration.

All of the medical assessments were conducted at the baseline visit, visit 5 (the end of the treatment) and the follow-up visit. For visits 3 and 4, vital signs and the laboratory tests were conducted, a compliance check (capsule count) was conducted and any adverse events were also monitored. The Ph.D candidate was responsible for assessment of participant compliance in taking the study medications. This was done by counting left-over capsules at each treatment visit and documenting them. In addtition, all unused medication and empty medication containers were collected from participants at the end of their study period.

10.4.5 Efficacy measurements

10.4.5.1 WOMAC visual analogue scale

The WOMAC VAS was conducted at three assessment visits (baseline, week 12, and week 16). The WOMAC VAS score was calculated for each of the three domains (pain, stiffness, physical function) and a WOMAC global score was computed as the unweighted mean of all 24 items. More detail about the WOMAC VAS may be found in Section 7.6.1 of Chapter 7.

10.4.5.2 The short form of health survey (SF-36)

The SF36 quality of life questionnaire was administered at the three assessment visits (baseline, week 12, and week 16). More detail about the SF-36 is set out in Section 7.6.4 of Chapter 7.

10.4.5.3 Physician global assessment

The Physician Global Assessment was conducted by the principal investigator, a rheumatologist of the Alfred Hospital. The Physician Global Assessment was administered at baseline (week 0) and week 12 post randomisation. More detail about the Physician Global Assessment can be found in Section 7.6.2 of Chapter 7.

10.4.5.4 Patient global assessment

The Patient Global Assessment is a validated, global health index that is self-administered. The patient global assessment was administered at baseline (week 0), week 12 post randomisation and week 16. More detail about patient global assessment may be found in Section 7.6.3 of Chapter 7.

10.4.5.5 Baeke physical activity questionnaire and diet diary

The Baeke Physical Activity questionnaire was administered at baseline (week 0) and week 12 post randomisation in order to monitor the potential change in physical activity.

A diet diary was completed by participants over four consecutive days in the first week after being randomised (week 0) and in the week prior to visit 5 (week 12).

10.5. Statistical analysis

Data was analysed using the SPSS (Statistical Package for the Social Sciences) version 17.0 for Windows. All primary and secondary endpoints can be regarded as continuous random variables and therefore similar analysis methods were undertaken. The intention-to-treat (ITT) principle was not used in this study. The principle refers in the event of a participant withdrawing from the study, the data of last observation carried forward (LOCF) will be used as the final visit data. However the ITT tends to be too conservative and biases the results toward equivalence for a treatment which is actually an inferior treatment, especially for small sample studies. It was suggested that ITT may be more useful in studies with long-term end-point follow up.(Lewis and Machin, 1993) The level of significance applied in the statistical analysis was 5%.

10.5.1 Sample size

Using a two sample equivalence test and based on previous data in a good quality OA study by Berman and colleagues (Berman et al., 1999) and a previous study on a Chinese herbal medicine upon which the Bai Niu Capsule was developed (Cao et al., 2004b), a mean difference in WOMAC score of 16.0 and standard deviation (SD) of 20.5 between the treatment group and placebo group at 12 weeks can demonstrate a statistically significant improvement. Sample size was calculated based on two-sided test with a 95% confidence level (α). The sample size calculation indicated that at least 56 participants (28 in each group) were required to give 80% power (1-β).

10.5.2 Test for normality of data and analysis of baseline data

Prior to the within-group and between-group analyses, normality of the data was assessed using the the Shapiro–Wilk W test.

Baseline data was compared between groups in two ways: one comparison was based on the data of all randomised participants at visit 2 and the other only included participants who completed the whole study (from visit 2 to visit 5). The Independent Samples T test was applied for normally distributed data, while the Mann-Whitney U test was applied for non-normal data.

10.5.3 Within- group analysis

Within-group analyses were conducted to assess change in the outcome variables. Where data was normal, the Paired Student T test was applied. Where normality of data was violated, the Wilcoxon's Signed-rank test was used. Significance of the tests was expressed by a p-value less than 0.05. As mentioned previously, if a participant withdrew from the study, the data of that participant was excluded from analysis.

10.5.4 Between- groups analysis

Between-groups analyses were conducted using the Independent Sample T Test. The use of this is justified for the following reasons.There was no difference between the two groups in the baseline data including participants' physical activity and dietary variables. In addition, there was no significant difference between the two groups for mean change of BMI, physical activity and nutrition intake throughout the trial. Thus there were no obvious potential confounding factors which would have required a more complex statistical model to be used.

Significance of the tests was expressed by a p- value less than 0.05. The change in each of the outcome variable from visit 2 to visit 5 and from visit 5 to visit 6 was compared between groups. Only data of participants who completed the whole 12 weeks of the study were included in the analyses.

10.6 Results

A total of 62 participants attended the initial screening visit, and of these, 47 were accepted into the study and randomised based on the inclusion and exclusion criteria. A total of 39 patients completed the study protocol: five dropped out from the herbal medicine group and three dropped out from the placebo group. One participant failed to attend the follow-up visit (placebo group).

The average compliance rate of capsules self-administration was 97.3% (herbal medicine group) and 94.6% (placebo group) respectively.

10.6.1 Baseline data

Of the 47 participants randomised into the study, 22 were randomised into the herbal medicine group (group BN) and 25 into the placebo group (group PL). There was no significant difference of gender proportion between the two groups: males and females were also almost evenly distributed in the two groups. In addition, based on the inclusion criteria of radiographic evidence, number of 'eligible knees' for each group were calculated. There was no significant difference in the mean number of affected knees. As per the inclusion/exclusion criteria, only those with grade 2 and grade 3 OA were accepted into the study, so the severity of the OA was the same across the two groups. See Tables 10.1 and 10.2 for details.

There was one patient in the placebo group who completed the treatment visits and only withdrew from the study at the follow-up visit; this participant was not counted as a drop-out case for the efficacy analysis.

Age, weight, body mass index (BMI), blood pressure, heart rate and the total score of the Baeke Physical Activity Questionnaire were compared to investigate if the participants in each group originated from the same study population. Data was analysed to check for normality also. Results are set out in Table 10.3. Diet of each participant at baseline was also analysed in order to distinguish if there were any nutritional differences between groups. The data showed that there was no significant difference between the two groups at baseline in terms of vital signs, physical activity and all dietary variables, except for total fat intake. However, there was no statistically significant difference between groups for all of the items when the analysis included all of those participants initially randomised into the study. See Table 10.3 for more information.

The data for BMI, Physical Activity Score and main dietary variables were compared at baseline (visit 2, week 0) and at the end of treatment (visit 5, week 12), in order to find out if these factors could be confounding factors. The results showed there was no significant difference between the two groups in the change in BMI, Physical Activity and diet during the study period. See Table 10.4 for more detail.

Table 10.1 Participants recruitment between two groups

Group	Total Participants	Male	Female	Drop-outs
BN	22	10	12	5
PL	25	13	12	3

Note: BN – Bai Niu Capsule group; PL – placebo control group

Table 10.2 Eligible knees between two groups

Group	Valid cases	Right knees	Left knees	Average eligible knees
BN	17	12	13	1.5
PL	22	16	15	1.4

Table 10.3 Tests for normal distribution and equality between the two groups

Item	Group	Mean ± SD (excluded drop-outs)	Sig. of W test	P Value	Mean ± SD (included drop-outs)	Sig. of W test	P Value
Age	BN	63.41 ± 10.28	0.837	0.13	62.09 ± 10.37	0.807	0.37
	PL	58.86 ± 11.29	**0.003**		60.28 ± 11.81	**0.007**	
Weight	BN	85.54 ± 18.19	0.811	0.98	85.35 ± 19.11	0.493	0.70
	PL	86.58 ± 22.93	**0.022**		87.76 ± 22.29	0.058	
BMI	BN	30.37 ± 6.16	0.669	0.96	30.30 ± 6.32	0.173	0.88
	PL	30.38 ± 5.83	**0.023**		30.56 ± 5.86	0.057	
Systolic Blood Pressure	BN	129.94 ± 14.55	0.204	0.72	128.05 ± 14.10	0.061	0.64
	PL	128.18 ± 15.37	0.851		130.08 ± 15.38	0.952	
Diastolic Blood Pressure	BN	76.06 ± 8.18	0.343	0.26	76.00 ± 7.31	0.107	0.08
	PL	79.36 ± 9.39	0.447		80.36 ± 9.27	0.244	
Heart Rate	BN	69.35 ± 11.91	0.003	0.24	68.14 ± 12.86	0.143	0.73
	PL	65.05 ± 10.65	0.474		66.88 ± 11.84	0.666	
Physical Activity Score	BN	6.65 ± 2.04	0.218	0.09	6.90 ± 1.92	0.401	0.23
	PL	7.66 ± 1.63	0.741		7.55 ± 1.70	0.510	
Kilo Joule Intake	BN	7743.65 ± 1838.91	0.331	0.19	7787.05 ± 2263.70	0.516	0.30
	PL	8559.48 ± 1904.22	0.394		8643.44 ± 1960.56	0.522	
Protein	BN	89.29 ± 21.06	0.377	0.80	90.65 ± 20.55	0.480	0.75
	PL	90.95 ± 18.94	0.066		92.56 ± 18.62	0.069	
Total Fat	BN	71.76 ± 22.28	0.389	**0.04 ***	72.40 ± 22.96	0.319	0.07
	PL	85.76 ± 19.10	0.225		84.80 ± 20.58	0.420	
Carbohydrate	BN	184.12 ± 48.66	0.105	0.55	194.65 ± 66.37	0.157	0.81
	PL	195.19 ± 60.70	1.000		195.75 ± 63.40	1.000	

Note: W test refers to the Shapiro–Wilk W test; *P* value < 0.05 (indicates significant difference) marked as *

Table 10.4 Mean change in baseline data between Visit 2 and Visit 5

Demographic data		Group	Mean Change ± SD	Sig. of W test	P Value
BMI		BN	-0.21 ± 0.42	0.676	0.32
		PL	0.05 ± 0.51	0.414	
Physical Activity Score		BN	0.19 ± 0.86	0.556	0.66
		PL	0.33 ± 1.03	0.117	
Diet	K Joule Intake	BN	-286.71 ± 1400.38	0.913	0.33
		PL	94.95 ± 1415.08	**0.023**	
	Protein	BN	-5.41 ± 16.99	0.447	0.45
		PL	-0.43 ± 22.04	0.306	
	Total fat	BN	-7.12 ± 14.20	0.536	0.32
		PL	-1.05 ± 21.43	0.463	
	Carbohydrate	BN	9.59 ± 43.92	0.254	0.69
		PL	4.14 ± 38.81	0.748	

Note: W test: Shapiro–Wilk W test

10.6.2 WOMAC assessment

10.6.2.1 Normality tests for WOMAC data

The WOMAC analysis included four indices: pain, stiffness, physical function, and a total score. Data was tested for normality at baseline (visit 2). Results indicated the score of each component for group BN and group PL were all normally distributed. There was no significant difference between the two groups on the pain index ($p = 0.25$), stiffness index ($p = 0.47$), physical function index ($p = 0.65$) and total score ($p = 0.50$) at baseline.

The scores of some of the WOMAC indices (such as the stiffness score of both group respectively, the pain score of the group BN) became non-normally distributed at the end of the study (visit 5). The data change within the two groups during the study period (visit 2 versus visit 5, and visit 5 versus. visit 6) was normally distributed except for the pain score in group PL. See Table 10.5 for more details.

Table 10.5 Mean WOMAC scores and tests for normality of data

Assessments & Groups		Valid Cases	Mean ± SD	Sig. of W test	P Value	Change between visits		Mean ± SD	Sig. of W test
V2 Pain	BN	17	174.92 ± 134.46	0.073	0.25	V5 – V2 Pain	BN	-44.27± 68.28	0.173
	PL	22	217.80 ± 95.15	0.877			PL	-54.94 ± 80.19	**0.039**
V2 Stiffness	BN	17	104.95 ± 63.76	0.152	0.47	V5 – V2 Stiffness	BN	-35.23 ± 46.03	0.324
	PL	22	118.42 ± 51.71	0.032			PL	-20.95 ± 54.79	0.577
V2 Physical Function	BN	17	786.19 ± 417.04	0.579	0.65	V5 – V2 Physical Function	BN	-190.15 ± 309.25	0.717
	PL	22	839.19 ± 316.42	0.501			PL	-168.07 ± 255.54	0.340
V2 Total Score	BN	17	1066.07±584.17	0.729	0.50	V5 - V2 Total	BN	-269.66 ± 374.11	0.647
	PL	22	1175.41±424.57	0.980			PL	-250.62 ± 343.25	0.232
V5 Pain	BN	17	130.65 ± 115.77	**0.012**		V6 –V5 Pain	BN	9.66 ± 57.14	0.807
	PL	22	162.39 ± 87.59	0.830			PL	42.06 ± 54.72	0.805
V5 Stiffness	BN	17	69.72 ± 56.48	**0.018**		V6 – V5 Stiffness	BN	15.05 ± 40.14	0.060
	PL	22	96.75 ± 56.53	**0.029**			PL	13.43 ± 34.00	0.164
V5 Physical Function	BN	17	596.04 ± 436.33	0.079		V6 – V5 Physical Function	BN	1.91 ± 249.84	0.475
	PL	22	665.65 ± 348.88	0.983			PL	126.57 ± 167.85	0.904
V5 Total Score	BN	17	796.41 ± 595.54	**0.045**		V6 – V5 Total	BN	26.63 ± 327.24	0.178
	PL	22	924.78 ± 460.17	0.939			PL	182.06 ± 229.00	0.849
V6 Pain	BN	17	140.31 ± 105.03	0.101					
	PL	21	204.81 ± 100.51	0.568					
V6 Stiffness	BN	17	84.77 ± 55.62	0.177					
	PL	21	109.22 ± 46.26	0.395					
V6 Physical Function	BN	17	597.96 ± 448.91	0.100					
	PL	21	793.13 ± 344.30	0.984					
V6 Total	BN	17	823.03 ± 594.47	0.159					

Score	PL	21	1107.17±462.04	0.784					

Note: BN – group BN; PL – group PL; W test refers to the Shapiro–Wilk W test

10.6.2.2 Within-group analysis of WOMAC

Within-group analyses were performed in order to investigate the effectiveness of the treatment based on the change in the WOMAC Index during the course of the trial. The mean change from visit 2 (baseline) to visit 5 (the end of treatment), and from visit 5 to visit 6 (follow-up visit) was measured.

For group BN, the pain index, stiffness index and total score at visit 5 were not normally distributed, therefore, the Wilcoxon's Signed-rank test was used for these analyses while the Independent Sample T test applied for physical function index. Analysis indicated that participants with knee OA had a significant reduction in pain ($p = 0.04$), stiffness ($p = 0.01$) and physical function ($p = 0.02$), and total WOMAC score ($p = 0.01$) at the end of the treatment. The mean total score had decreased from 1066.07 ± 584.17 to 796.41 ± 595.54. Although the score slightly increased at the follow-up visit, there was no statistically significant change compared with the data of visit 5. In another words, the patients' pain, stiffness and physical function remained in a stable condition after stopping the treatment for one month.

Similar findings were seen in the PL group. Patients showed a positive response in the relief of pain, physical function and total score at visit 5. Total score was significantly decreased from 1175.41 ± 424.57 to 924.78 ± 460.17 ($p = 0.00$). However, the symptoms of knee OA seemed to recur immediately when the sham treatment was stopped. The total score of WOMAC ($p = 0.00$), pain index ($p = 0.00$) and physical function ($p = 0.00$) were all found to increase dramatically at visit 6 (the follow-up visit), one month after the treatment. Although the stiffness index did not rebound significantly ($p = 0.22$), it did not significantly change (from visit 2 to visit 5) in the first place. The total score at visit 6 (1107.17 ± 462.04) was almost back to the same level at the visit 2 (baseline visit, 1175.41 ± 424.57). See Table 10.6 for more details.

Table 10.6 Within-group analysis of WOMAC index

Group & Time		WOMAC Index	Visit	Valid (n)	Mean ± SD	P value
BN	Visit 5 vs. Visit 2	Pain	V2	17	174.92 ± 134.46	**0.04 ***
			V5	17	130.65 ± 115.77	
		Stiffness	V2	17	104.95 ± 63.76	**0.01 ***
			V5	17	69.72 ± 56.48	
		Physical function	V2	17	786.19 ± 417.04	**0.02 ***
			V5	17	596.04 ± 436.33	
		Total Score	V2	17	1066.07 ± 584.17	**0.01 ***
			V5	17	796.41 ± 595.54	
	Visit 6 vs. Visit 5	Pain	V5	17	130.65 ± 115.77	0.59
			V6	17	140.31 ± 105.03	
		Stiffness	V5	17	69.72 ± 56.48	0.21
			V6	17	84.77 ± 55.62	
		Physical function	V5	17	596.04 ± 436.33	0.98
			V6	17	597.96 ± 448.91	
		Total Score	V5	17	796.41 ± 595.54	0.96
			V6	17	823.03 ± 594.47	
PL	Visit 5 vs. Visit 2	Pain	V2	22	217.80 ± 95.15	**0.00 ***
			V5	22	162.39 ± 87.59	
		Stiffness	V2	22	118.42 ± 51.71	0.15
			V5	22	96.75 ± 56.53	
		Physical function	V2	22	839.19 ± 316.42	**0.00 ***
			V5	22	665.65 ± 348.88	

		Total Score	V2	22	1175.41 ± 424.57	**0.00 ***
			V5	22	924.78 ± 460.17	
	Visit 6 vs. Visit 5	Pain	V5	22	162.39 ± 87.59	**0.00 ***
			V6	21	204.81 ± 100.51	
		Stiffness	V5	22	96.75 ± 56.53	0.22
			V6	21	109.22 ± 46.26	
		Physical function	V5	22	665.65 ± 348.88	**0.00 ***
			V6	21	793.13 ± 344.30	
		Total Score	V5	22	924.78 ± 460.17	**0.00 ***
			V6	21	1107.17 ± 462.04	

Note: *P* value <0.05 (indicates significant difference) marked as *

10.6.2.3 Between-groups analysis of WOMAC

There was no significant difference between the two groups when comparing the change from visit 2 to visit 5 and from visit 5 to visit 6 for the total score and the individual indices (pain, stiffness and physical function), although strong trends ($p<0.1$) were observed in pain, physical function and total score during the one month follow-up. Results are set out in Table 10.7.

Table 10.7 Between-group analysis of WOMAC index

Time	Index	Group	Valid (n)	Mean Change ± SD (between visits)	P value
Visit 5 vs. Visit 2	Pain	BN	17	-44.27± 68.28	0.70
		PL	22	-54.94 ± 80.19	
	Stiffness	BN	17	-35.23 ± 46.03	0.41
		PL	22	-20.95 ± 54.79	
	Physical function	BN	17	-190.15 ± 309.25	0.85
		PL	22	-168.07 ± 255.54	
	Total Score	BN	17	-269.66 ± 374.11	0.87
		PL	22	-250.62 ± 343.25	
Visit 6 vs. Visit 5	Pain	BN	17	9.66 ± 57.14	0.08
		PL	21	42.06 ± 54.72	
	Stiffness	BN	17	15.05 ± 40.14	0.89
		PL	21	13.43 ± 34.00	
	Physical function	BN	17	1.91 ± 249.84	0.08
		PL	21	126.57 ± 167.85	
	Total Score	BN	17	26.63 ± 327.24	0.09
		PL	21	182.06 ± 229.00	

Note: BN – Bai Niu Capsule group; PL – placebo control group

10.6.3 SF-36 health survey

10.6.3.1 Normality tests for SF-36 data

The SF-36 health survey included two components, a physical domain and a mental domain. The scores for each domain were normally distributed for group BN and group PL. There was no significant difference between two groups for either domain at baseline (physical domain $p = 0.82$, mental domain $p = 0.37$). See Table 10.8.

The change in scores (for each domain) throughout the trial (visit 2 versus visit 5, and visit 5 versus visit 6) were normally distributed within each group, except for the physical component in group BN. Therefore, non-parametric statistical analysis was used for this item in the within-group analysis.

The data quality of the SF-36 was also assessed by the response consistency index (RCI) which reveals if the measurement really indicates the health condition of the participants and accuracy of the data. The best RCI score is zero while the worst score is 15. For group data, like in this study, the percentage of consistent responses is the measurement of data quality. The data check showed the average percentage of RCI score zero in group BN was 90% and group PL was 97%, therefore it indicated that the SF-36 data was collected in a reliable and accurate way in this study. See Table 10.9 for more details.

Table 10.8 SF-36: tests for normality of data

Assessments & Groups		Valid Cases	Mean ± SD	Sig. of W test	P Value	Change between visits		Mean ± SD	Sig. of W test
V2 Physical Sum	BN	17	37.56 ± 10.50	0.149	0.82	V5 – V2 Physical Sum	BN	0.60 ± 8.12	**0.010**
	PL	22	38.26 ± 8.59	0.308			PL	1.62 ± 6.20	0.463
V2 Mental Sum	BN	17	53.91 ± 8.51	0.913	0.37	V5- V2 Mental Sum	BN	-1.48 ± 9.37	0.497
	PL	22	51.36 ± 8.92	0.370			PL	3.04 ± 8.03	0.112
V5 Physical Sum	BN	17	38.17 ± 11.13	0.526		V6- V5 Physical Sum	BN	2.64 ± 6.81	0.821
	PL	22	39.88 ± 7.74	0.644			PL	-0.60 ± 5.78	0.842
V5 Mental Sum	BN	17	52.43 ± 9.04	0.643		V6- V5 Mental Sum	BN	-1.32 ± 7.75	0.543
	PL	22	54.41 ± 9.29	**0.003**			PL	-3.49 ± 7.97	0.202
V6 Physical Sum	BN	17	40.80 ± 11.18	0.310					
	PL	21	39.16 ± 8.70	0.616					
V6 Mental Sum	BN	17	51.11 ± 9.92	0.899					
	PL	21	51.25 ± 9.05	0.664					

Note: BN – the group BN; PL – the group PL; W test refers to the Shapiro–Wilk W test

Table 10.9 Percentage of response consistency index (RCI) score of zero

Group	Visit 2 (%)	Visit 5 (%)	Visit 6 (%)	Average (%)
BN	82	94	94	90
PL	95	100	95	97

Note: BN – Bai Niu Capsule group; PL – placebo control group

10.6.3.2 Within-group analysis of SF-36

The within-group analysis was conducted by analysing the index change from visit 2 (baseline) to visit 5 (the end of treatment), and from visit 5 to visit 6 (follow-up visit). For group BN, there was no significant change in the general health condition between visit 2 and visit 5 and between visit 5 and visit 6. Although the physical component score slightly increased from visit 2 to visit 5 and kept rising to visit 6, while the mental component slightly decreased, this was not statistically significant. That means that the health status of participants remained stable in this group.

Group PL also showed no significant change in physical health throughout the trial. But mental health improved significantly at the end of treatment (visit 5), from 51.36 ± 8.92 to 54.41 ± 9.29 ($p = 0.02$), indicating a positive response in this quality of life domain. Mental health score decreased by the end of the follow-up period, however this change was not statistically significant ($p = 0.09$). See Table 10.10 for more details.

Table 10.10 Within-group analysis of SF-36

Group & Time		Index	Visit	Valid (n)	Mean ± SD	P value
BN	Visit 5 vs. Visit 2	Physical score	V2	17	37.56 ± 10.50	0.76
			V5	17	38.17 ± 11.13	
		Mental score	V2	17	53.91 ± 8.51	0.52
			V5	17	52.43 ± 9.04	
	Visit 6 vs. Visit 5	Physical score	V5	17	38.17 ± 11.13	0.13
			V6	17	40.80 ± 11.18	
		Mental score	V5	17	52.43 ± 9.04	0.49
			V6	17	51.11 ± 9.92	
PL	Visit 5 vs. Visit 2	Physical score	V2	22	38.26 ± 8.59	0.23
			V5	22	39.88 ± 7.74	
		Mental score	V2	22	51.36 ± 8.92	**0.02***
			V5	22	54.41 ± 9.29	
	Visit 6 vs. Visit 5	Physical score	V5	22	39.88 ± 7.74	0.64
			V6	21	39.16 ± 8.70	
		Mental score	V5	22	54.41 ± 9.29	0.09
			V6	21	51.25 ± 9.05	

Note: *P* value <0.05 (indicates significant difference) marked as *

10.6.3.3 Between-groups analysis of SF-36

Although there was an improvement in mental health condition in group PL during the treatment period, the between-groups analyses showed there was no significant difference between two groups when comparing the change from visit 2 to visit 5 in this component ($p = 0.11$). As for the change in physical health score, there was no statistically significant difference between the two treatment groups, for the change from visit 2 to visit 5 ($p = 0.46$) nor the change from visit 5 to visit 6 ($p = 0.12$).

See Table 10.11 for more details.

Table 10.11 Between-group analysis of SF-36

Time	Index	Group	Valid (n)	Mean ± SD (between visits)	P value
Visit 5 vs. Visit 2	Physical score	BN	17	0.60 ± 8.12	0.46
		PL	22	1.62 ± 6.20	
	Mental score	BN	17	-1.48 ± 9.37	0.11
		PL	22	3.04 ± 8.03	
Visit 6 vs. Visit 5	Physical score	BN	17	2.64 ± 6.81	0.12
		PL	21	-0.60 ± 5.78	
	Mental score	BN	17	-1.32 ± 7.75	0.41
		PL	21	-3.49 ± 7.97	

10.6.4 Patient and physician global assessments

10.6.4.1 Normality test for data

Baseline data for the Patient Global assessment and Physician Global Assessment was tested for normality and equality. Results indicated that the data was normally distributed. There was no significant difference at baseline between the two groups from the patients' perspective (Patient Global Assessment) and from the physician's perspective (Physician Global Assessment). See Table 10.12 for more details.

Table 10.12 Patient Global Assessment and Physician global assessment data: tests for normality of data

Assessment & Groups		Valid Cases	Mean ± SD	Sig. of W test	P Value	Change between visits		Mean ± SD	Sig. of W test
V2 Patient	BN	17	54.82 ± 23.54	0.610	0.20	V5 – V2 Patient	BN	10.94 ± 32.05	0.614
	PL	22	44.36 ± 25.75	0.660			PL	11.09 ± 25.83	0.451
V5 Patient	BN	17	65.76 ± 25.51	0.274		V6- V5 Patient	BN	-3.53 ± 26.40	0.133
	PL	22	55.45 ± 23.90	0.972			PL	-6.48 ± 19.95	0.203
V6 Patient	BN	17	62.24 ± 26.24	0.375					
	PL	21	48.62 ± 25.68	0.232					
V2 Physician	BN	11	1.64 ± 0.81	**0.002**	0.24	V5 – V2 Physician	BN	0.36 ± 1.21	**0.033**
	PL	19	1.95 ± 0.71	**0.002**			PL	0.26 ± 1.05	**0.009**
V5 Physician	BN	11	2.00 ± 0.78	**0.025**					
	PL	19	2.21 ± 0.86	**0.003**					

Note: BN – the group BN; PL – the group PL; W test refers to the Shapiro–Wilk W test

10.6.4.2 Within-group analysis of patient and physician global assessments

The mean VAS for the Patient Global Assessment appeared to increase at the end of the treatment (visit 5) in both groups and decrease during the one month following. However, these changes did not reach statistical significance ($p > 0.05$). As for the Physician Global Assessment, it also failed to demonstrate a significant change throughout the study. See Table 10.13 for more details.

Table 10.13 Within-group analysis: Patient Global Assessment and Physician Global Assessment

Group & Time		Index	Visit	Valid (n)	Mean ± SD	P value
BN	Visit 5 vs. Visit 2	Patient Global Assessment	V2	17	54.82 ± 23.54	0.18
			V5	17	65.76 ± 25.51	
	Visit 6 vs. Visit 5	Patient Global Assessment	V5	17	65.76 ± 25.51	0.59
			V6	17	62.24 ± 26.24	
PL	Visit 5 vs. Visit 2	Patient Global Assessment	V2	22	44.36 ± 25.75	0.06
			V5	22	55.45 ± 23.90	
	Visit 6 vs. Visit 5	Patient Global Assessment	V5	22	55.45 ± 23.90	0.15
			V6	21	48.62 ± 25.68	
BN	Visit 5 vs. Visit 2	Physician Global Assessment	V2	11	1.64 ± 0.81	0.33
			V5	11	2.00 ± 0.78	
PL	Visit 5 vs. Visit 2	Physician Global Assessment	V2	19	1.95 ± 0.71	0.31
			V5	19	2.21 ± 0.86	

10.6.4.3 Between-groups analysis of Patient Global Assessment and Physician Global Assessments

Between-groups analyses of the Patient Global Assessment and Physician Global Assessment did not reveal a significant difference between the two groups. See Table 10.14 for more details.

Table 10.14 Between-group analysis: Patient Global Assessment and Physician Global Assessment

Index	Time	Assessment items	Group	Valid (n)	Mean ± SD (change between visits)	P value
Patient Global Assessment	Visit 5 vs. Visit 2	Global score	BN	17	10.94 ± 32.05	0.99
			PL	22	11.09 ± 25.83	
	Visit 6 vs. Visit 5	Global score	BN	17	-3.53 ± 26.40	0.70
			PL	21	-6.48 ± 19.95	
Physician Global Assessment	Visit 5 vs. Visit 2	Global score	BN	11	0.36 ± 1.21	0.49
			PL	19	0.26 ± 1.05	

10.7 Discussion

This pilot study was the first randomised, double-blind and placebo-controlled trial of a Chinese herbal medicine in the treatment of Australian patients with OA of the knee. The trial was conducted in a scientifically rigorous manner based on the CONSORT (Consolidated Standards of Reporting Trials) Guidelines (Begg et al., 1996, Moher et al., 2001). The primary outcome variable, the WOMAC index, is an OA disease-specific instrument, so it more accurately reflects the efficacy of a therapy for OA patients.(Salaffi et al., 2005)

The within-group analysis showed that OA symptoms had significantly improved at the end of the herbal treatment as measured by a reduced WOMAC score for knee pain, stiffness, physical activities and total score. When the herbal medicine was ceased, the scores for pain, stiffness and physical activity did not show a significant increase or rebound. This suggests that the effectiveness of the herbal medicine was maintained at least in the one month follow-up period. However, the placebo was also found to reduce the WOMAC scores of pain, physical activity and total score (but not the stiffness score) over 12 weeks. Contrary to the herbal group, this improvement disappeared quickly in the placebo group and there were significant rebound in the WOMAC scores of pain ($p < 0.01$), physical activity ($p < 0.01$) and total score ($p < 0.01$). However, there was no statistical significance between the two groups in terms of WOMAC scores for pain, stiffness physical activity and total score.

Although there was no difference found between the two groups in the WOMAC score, it cannot be concluded directly that the efficacy of the Chinese herbal medicine (Bai Niu Capsule) was the same as a placebo effect. There are a few reasons. Firstly, there were fewer participants recruited into this trial than the designed sample size. It was calculated that 28 participants in each group could provide an 80% power for the statistical analysis of an assumed very large population. However, there were only 47 participants recruited into the study and sample sizes were unequal. Recalculation using the actual sample size indicated the study had only a 62% power to detect a significant difference in the primary outcome variable. However, the data of this underpowered study still suggests that there was a sustained therapeutic effect of the herbal medicine in the follow-up period which

was not seen in the placebo group. In addition, not only was there no significant change of the stiffness score in the placebo group throughout the trial, but also the changes of the pain score, physical functions and total score in this group during the follow-up period actually indicated a trend that came close to statistical significance and may have reached this if there had been more participants in this study. For example, the between- group analysis showed that the p value for the physical function score was 0.08 in the follow-up period (which was close to the level of significance set in this study; $p = 0.05$). The mean change in physical function score in the herbal medicine group was 1.91 while in the placebo group it was 126.57, and the standard deviation of this data was 249.84 in the herbal medicine group and 167.85 in the placebo group. It is reasonable to assume that if the number of participants was increased, the standard deviation would normally be smaller, and then the statistical difference between two groups may have been reached. A similar situation was also found for the score of pain, and total score in the follow-up period. (See Table 10.7 for more details)

Secondly, the trial period of 12 weeks was still a short term treatment for OA of the knee. The genuine effectiveness of this herbal capsule, a kind of slow acting medicine, may need a longer treatment period for its effects to fully emerge. The reactions within each group at the follow-up visit are suggestive of this. If the treatment period could have been longer, it is possible that a significant difference between groups may have been emerged.

The Patient Global Assessment and SF-36 are secondary assessment tools, with the main emphasis on the general health status of participants. In this study, the Patient Global Assessment did not indicate a significant change in the general health condition of participants, no matter which study medication was received. This is not an unreasonable finding, after all, the majority of participants have a history of knee OA of more than 10 years and it may be difficult to improve the health status in a chronic disease in a three-month treatment period. The change in participants' general feelings about the impact of OA on daily life for both groups showed a positive trend throughout the trial. This could be because the participants simply believed they had received a treatment which could be of benefit to their health. The data also showed that the score in the two groups both increased (improved) at the end of the treatment and decreased in the follow-up period,

though these changes failed to demonstrate a statistical significance. (See Table 10.13 for more details) The VAS score of the Patient Global Assessment of the herbal medicine group increased indicating, at least, that the herbal medicine did not cause a negative impact on the participants' health.

The SF-36 assessment also did not show a significant change in participants' physical health in either group during the study period. However, an interesting finding was that the mental health score of the placebo group significantly improved at the end of the treatment and did not decrease significantly in the follow-up period. This could be interpreted as representing a typical placebo effect. The between- groups analysis indicated that there was no difference in scores between the groups.

Although the Physician Global Assessment may be useful for measuring the efficacy of symptom-modifying drugs (Collins et al., 2001), in this study, we did not collect enough data to ascertain a reliable result in terms of the rheumatologist's perspective, due to time constraints of the practitioner.

The previous study that investigated a herbal formula upon which the Bai Niu Capsule was developed (Cao et al., 2004b) also failed to show a superior effectiveness (as measured by the WOMAC Index) of the study herbal formula compared with another Chinese herbal medicine. However, there was no evidence provided of the efficacy of the comparison CHM formula, so it was difficult to conclude if the effectiveness of two formulae was due to the placebo effect or a therapeutic effect. Therefore, the clinical significance of their study is actually not clear. Their study did find a significant improvement in pain, stiffness and phyisical activity in the study herbal medicine group in a four-week treatment period, which was particularly obvious during the period between week 2 and week 4.(Cao et al., 2004b)

In a summary, the efficacy of the Bai Niu capsule in the treatment for knee OA was not significantly different from placebo in this small sample trial. However the Bai Niu capsule showed effectiveness in relief of OA symptoms, especially stiffness of knee joints which was maintained one month after the cessation of the treatment. The Chinese

herbal medicine formula also did not cause a negative impact on the health of participants throughout the trial (see Chapter 11).

10.8 Limitations of the study

This study was a pilot study with some limitations which may have affected the results. As a small budget Ph.D study, there was limited time and resources to to recruit enough participants to achieve the required sample size. This trial was subjected to prolonged scrutiny by the Human Research Ethics Committee of the Alfred Hospital, resulting into late recruitment of participants. In addition, the slow recruitment was also partly due to lack of funds for advertising, time and availability constraints of the rheumatologist and availability of the clinical facilities. These factors prohibited an efficient recruitment in the limited Ph.D study period. Therefore, in the end, the study was only powered to detect a 62% change in the primary outcome variable (WOMAC Index) based on 17 valid participants in the herbal medicine group and 22 in the placebo group, when the study actually needed 28 participants in each group based on the sample size calculation.

In addition, there was also no pharmaceutical company in Australia which could produce the Chinese herbal medicine granules according to GMP standards. Therefore, we had to seek a manufacturer in Taiwan. This process took alomost one year before the study capsules were eventually shipped to the trial pharmacy. As a trial medicine, the Bai Niu capsule had a two year expiry period according to the medicine manufacturing regulatory requirements. Recruitment had to be ceased when the study medicines were close to the expiry date (November 2010).

The trial period of 12 weeks is still considered short term treatment for OA of the knee. The genuine effectiveness of this kind of treatment, being herbal medicine and slow acting, may need a longer treatment period for potential benefits to fully emerge. The herbal formula was not an existing medicine on the market. The actual dose of the herbal medicine in the granule form used in the study was less than the traditional raw herb dosages which could result in a weaker therapeutic effect. The concentration ratio for the granules used in the study was 1:3.86 (concentrated granules versus equivalent raw herbs) based on the manufacturing technique utilised. Therefore, the actual dose of the

concentrated herbal medicine corresponded to approximately 1/5 dosage of traditional raw herbs. Manufacture was based on the capacity of each capsule (500mg), the ratio between the herbal extract and excipient (1:1.5) and a dosage of 15 capsules a day. It is unknown at this stage if raw herbs could be more effective than granules. More studies need to be conducted in order to investigate the real efficacy of this Chinese medicine formula, with larger numbers and over a longer time period.

10.9 Conclusion

The study was the first randomised, double-blind and placebo-controlled trial of a Chinese herbal medicine formula in the treatment of Australian patients with OA of the knee. This formula was designed based on a Chinese medicine theory that OA should be considered as a combined Syndrome of Wei Syndrome and Bi Syndrome.

Statistical analyses showed Bai Niu capsule was not significantly different from placebo in term of the change of outcome variables measured. However, as measured by the WOMAC score, there was a significant effectiveness in relief of OA symptoms in the Bai Niu group throughout the trial, especially for reducing stiffness of knee joints which was not seen in the placebo group.

Based on the findings from the previous study from which the current formula was developed (see Cao et al., 2004b on Table 5.1), Dang Gui and Huai Niu Xi were added into the formula in order to strengthen the effect on nourishing the Liver. This trial revealed a trend of a decrease in the WOMAC score for stiffness in the herbal medicine group only, which may not necessarily be due to the placebo effect. In CM, knee stiffness (a sign of Wei Syndrome) is regarded as a lack of Blood (which has a nourishing function) and this function is governed by the Liver. This effect on alleviating knee stiffness in particular within the herbal medicine group may give some measure of support to the theory that OA should be treated as a combined Wei Syndrome and Bi Syndrome and that the therapeutic emphasis should be on nourishing the Liver and tonifying the Kidney rather than tonifying Kidney, though it is not conclusive. However, more longer-term and large scale studies are required to verify the theory.

Chapter 11 Safety of the Chinese herbal medicine

11.1 Introduction

Although there are many different reasons why people choose to use complementary and alternative medicine (CAM), such as dissatisfaction with conventional medicine, need of personal health, and people's beliefs, (Eastwood, 2000) the safety of CAM has been of great interest to patients and physicians. As required by Good Clinical Practice guidelines, any side effects or potential adverse event (s) related to this herbal product or placebo treatment were tightly monitored during the study. An adverse event (AE) was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the trial. In this study, laboratory tests including serum chemistry, haematology, and urinalysis, 12-lead electrocardiogram, concomitant medication review and adverse event reports (incidence and severity) were used to analyse the safety of the Chinese herbal medicine.

11.2 Methods of safety monitoring

11.2.1 Definition of adverse events

An AE includes:

1) Significant or unexpected worsening or exacerbation of the condition/indication under study

2) Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

3) New conditions detected or diagnosed after investigational product administration, even though it may have been present prior to the start of the study.

4) Signs, symptoms, or the clinical sequel of a suspected interaction.

5) Signs, symptoms, or the clinical sequel of a suspected overdose of either investigational product or a concurrent medication (overdose itself was not regarded as an AE).

In addition, a serious adverse event (SAE) refers to any untoward medical occurrence that, at any dose:

a) results in death;

b) is life-threatening (referring to an event in which the subject was at risk of death at the time of the event, not referring to an event, which hypothetically might have caused death, if it were more severe.);

c) requires hospitalisation or prolongation of existing hospitalisation; Hospitalisation refers to that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. In addition, complications that occur during hospitalisation are regarded as AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, then the event is serious.

d) results in disability/incapacity; The term disability means a substantial disruption of a person's ability to conduct normal life functions, not including experiences of relatively minor medical significance which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

All AEs and SAEs, regardless of relationship to study medications or the trial procedure, were recorded by the investigator (the Ph.D candidate). Abnormal laboratory findings or other abnormal assessments (e.g. vital signs) judged by the investigators (the rheumatologist and/or the Ph.D candidate) as clinically significant were recorded as AEs or SAEs if they met the definition of an adverse event. The judgments were made based on the medical and scientific judgment of the investigators in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant.

11.2.2 Procedure for detecting adverse events

Participants were monitored at each visit during the study for the occurrence of AEs/SAEs, including the follow-up (post-study) visit, and they were asked the following standard questions:

i. How are you feeling?

ii. Have you had any medical problems since your last visit?

iii. Have you taken any medications since your last visit?

Vital signs, blood pressure (BP), heart rate (HR) assessments, and concomitant medications and adverse events were recorded at each visit (visit 1-6), while the laboratory tests including haematology, serum chemistry (following a standard eight hour fasting period) and urinalysis (dipstick) were conducted at the screening visit (visit 1) and three treatment period visits (visit 3-5). In addition, each participant's electrocardiogram (ECG) was monitored at the screening visit (visit 1) and at the end of the treatment (visit 5), and assessed by the principal investigator (a senior rheumatologist). A comparison of the values and results throughout all measurement visits was performed to identify any parameters that may have changed from pre-study levels.

The items of blood tests included a full blood examination, such as white blood cells (WBC), red blood cells (RBC), haemoglobin (HGB), haematocrit (HCT), and platelets (PLT); electrolytes analysis, such as sodium (Na^+), potassium (K^+), calcium (Ca); renal function tests including as blood urea nitrogen (BUN) andcreatinine (Cr); liver function tests such as aspartate transaminase (AST), alanine transaminase (ALT), bilirubin (BIL). Other items included glucose (GLU), cholesterol (CHOL), triglycerides (TG), creatine kinase (CK), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), prothrombin time (PT), and activated partial thromboplastin time (APTT).

The urinalysis included:pH, glucose (GLU), protein (PRO), occult blood (BLO), leukocytes (LEU) and ketones (KET). All of the blood samples were tested by the central laboratory of the Alfred Hospital and urine samples were tested by the laboratory of the Centre for Clinical Trials, Nucleus Network, Australia.

11.3 Results of the safety monitoring

The safety data has been separated into four sections: change in vital signs, results of laboratory tests, ECG diagnoses, and clinical adverse events. For the numerical data such as vital signs and laboratory tests, the difference between the two groups at baseline was

analysed by the Independent Sample T test. An ANOVA test was conducted for the change in safety outcome variable within each group throughout all assessment visits. The Mann-Whitney U test and the Friedman test were applied for non-parametric data (urinalysis). All statistical analyses were performed by SPSS version 17.0 for Windows.

11.3.1 Vital signs

Vital signs were monitored at a total of six clinical visits. The key vital signs of this clinical trial were BMI (body mass index), blood pressure and heart rate. There was no significant difference between the two groups at baseline (See Table 11.1 for more details). Participants did not show a significant change of these vital signs throughout the whole trial, whether taking the herbal medicine (group BN) or the placebo (group PL), with the exception of heart rate which showed statistically significant changes in both groups at times during the six visits period (See Table 11.1 for more details). However, the data of the individual visits indicated these were all within the normal range and were not judged to be of clinical significance (See Table 11.2 for more details).

Table 11.1 Changes in key vital signs

Vital signs	Group	Baseline (mean ± SD)	*P* Value 1	*P* Value 2
BMI	BN	30.37 ± 6.16	0.96	0.12
	PL	30.38 ± 5.83		0.22
Systolic BP	BN	129.94 ± 14.55	0.72	0.72
	PL	128.18 ± 15.37		0.28
Diastolic BP	BN	76.06 ± 8.18	0.26	0.42
	PL	79.36 ± 9.39		0.22
Heart rate	BN	70.69 ± 10.62	0.24	**0.00 ***
	PL	70.76 ± 10.61		**0.00 ***

Note:

P value 1 – Significance between groups at the baseline

P value 2 – Significance within-group throughout six visits

* - Statistical significance ($p < 0.05$)

Table 11.2 Change in heart rate during the trial

Visit	Group BN		Group PL	
	Mean ± SD	Valid cases	Mean ± SD	Valid cases
Visit 1	69.56 ± 12.27	16	64.71 ± 10.79	21
Visit 2	70.69 ± 10.62	16	70.76 ± 10.61	21
Visit 3	65.00 ± 8.40	16	65.52 ± 9.57	21
Visit 4	64.63 ± 7.80	16	66.81 ± 8.57	21
Visit 5	66.25 ± 9.31	16	62.24 ± 9.77	21
Visit 6	71.56 ± 9.51	16	71.71 ± 13.13	21

Note: missing data was excluded from the analysis. One patient in the group BN failed to attend at visit 3, and one patient in the group PL was absent at visit 6.

11.3.2 Blood and urine tests

11.3.2.1 Blood tests

Blood and urine tests were conducted at four visits (baseline, and visits 3-5) and were used as the selection criteria for eligible participants and for monitoring the safety of the trial. Data at baseline showed there were no significant differences between the two groups in terms of the full blood examination, liver function tests, renal function tests, and biochemistry and coagulation tests. Most of the results of the blood tests were also within the normal range, based on the mean values. See Table 11.3 for more details.

There was no significant change in the majority of test items throughout the four visits, except for the following: red blood cells, haemoglobin, haematocrit and potassium in the placebo group, and glucose in the herbal medicine group. (See Table 11.3) However, an examination of these tests in detail failed to demonstrate that the results of each visit were abnormal. The difference at a particular visit was not consistent across all visits, and was likely due to chance. (See Table 11.4 for more details)

Table 11.3 Changes in blood tests

Test items	Normal range	Group	Baseline (mean ± SD)	*P* Value1	*P* Value2
WBC	3.90 – 12.70 $^{10\text{^}9/L}$ (F)	BN	6.15 ± 1.80	0.85	0.76
	4.60 – 10.50 $^{10\text{^}9/L}$ (M)	PL	6.27 ± 1.54		0.34
RBC	3.60 – 5.30 $^{10\text{^}12/L}$ (F)	BN	4.51 ± 0.21	0.45	0.69
	4.00 – 5.70 $^{10\text{^}12L}$ (M)	PL	4.43 ± 0.39		**0.01 ***
HGB	113 – 159 $^{g/L}$ (F)	BN	140.25 ± 11.70	0.37	0.74
	122 – 170 $^{g/L}$ (M)	PL	136.95 ± 12.60		**0.00 ***
HCT	0.32 – 0.42 $^{L/L}$ (F)	BN	0.41 ± 0.03	0.18	0.60
	0.36 – 0.49 $^{L/L}$ (M)	PL	0.40 ± 0.03		**0.01 ***
PLT	150 – 396 $^{10\text{^}9/L}$	BN	212.19 ± 43.68	0.55	0.53
		PL	222.05 ± 27.20		0.21

Na	135 – 143 mmol/L	BN	140.06 ± 1.44	0.20	0.88
		PL	139.24 ± 2.55		0.75
K^+	3.5 – 5.0 mmol/L	BN	4.04 ± 0.29	0.72	0.57
		PL	4.03 ± 0.31		**0.00 ***
Ca	2.23 – 2.50 mmol/L	BN	2.35 ± 0.09	0.81	0.32
		PL	2.33 ± 0.10		0.80
BUN	3.0 – 8.0 mmol/L (F) 4.0 – 9.0 mmol/L (M)	BN	6.21 ± 1.59	0.68	0.52
		PL	6.02 ± 1.58		0.39
Cr	45 – 80 umol/L (F) 60 – 105 umol/L (M)	BN	71.19 ± 14.25	0.80	0.81
		PL	72.33 ± 17.78		0.81
AST	12 – 42 U/L	BN	21.63 ± 9.48	0.76	0.68
		PL	21.10 ± 4.24		0.46
ALT	9 – 36 U/L (F) 12 – 52 U/L (M)	BN	21.50 ± 10.65	0.70	0.71
		PL	23.76 ± 9.84		0.92
BIL	< 14 umol/L (F) < 23 umol/L (M)	BN	10.56 ± 9.01	0.61	0.08
		PL	11.81 ± 6.37		0.15
GLU	4.0 – 7.0 mmol/L	BN	4.87 ± 0.51	0.82	**0.02 ***
		PL	4.85 ± 0.51		0.38
CHOL	< 5.5 mmol/L	BN	4.96 ± 0.96	0.59	0.55
		PL	5.08 ± 0.89		0.18
TG	< 2.0 mmol/L	BN	1.35 ± 0.92	0.13	0.66
		PL	1.10 ± 0.47		0.08
CK	40 – 200 U/L (F) 60 – 285 U/L (M)	BN	116.88 ± 62.29	0.77	0.81
		PL	112.29 ± 52.02		0.12
ESR	1 – 20 mm/1hr (F) 1 – 10 mm/1hr (M)	BN	15.50 ± 14.45	0.23	0.76
		PL	11.24 ± 4.93		0.66

PT	10.6 – 15.3 sec	BN	15.00 ± 4.31	0.16	0.23
		PL	13.52 ± 0.62		0.15
APTT	26.0 – 38.0 sec	BN	30.69 ± 3.98	0.55	0.37
		PL	29.68 ± 3.22		0.42

Note: F – female; M - male

P 1 - Significance between two groups at baseline

P 2 - Significance within-group throughout four visits

* - Statistical significance ($p < 0.05$)

Table 11.4 Details of the blood tests with significant changes during the trial

Visit	GLU (Group BN)	RBC (Group PL)	HGB (Group PL)	HCT (Group PL)	K^+ (Group PL)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Visit 1	4.87 ± 0.51	4.43 ± 0.39	136.95 ± 12.60	0.40 ± 0.03	4.03 ± 0.31
Visit 3	5.33 ± 1.01	4.52 ± 0.43	140.29 ± 14.79	0.41 ± 0.04	4.22 ± 0.32
Visit 4	5.14 ± 1.06	4.59 ± 0.38	142.19 ± 13.78	0.41 ± 0.04	4.23 ± 0.36
Visit 5	5.12 ± 0.85	4.49 ± 0.41	139.19 ± 13.70	0.41 ± 0.04	4.17 ± 0.32

11.3.2.2 Urine tests

A ranking system was adapted into the statistical analyses for the urinalysis items because the results from the dipstick analysis were based on grades, rather than numbers. Therefore, the Mann-Whitney U test was used for the test of baseline data and the Friedman test used for analysing variance amongst the four visits.

There was no difference between the two groups at baseline, nor were any sigificant changes in urinalysis items measured in this study. Although the blood test showed there was a significant change of blood glucose in the herbal medicine group, urinalysis

indicated urine glucose remained negative throughout the four visits for every participant. Thus, no adverse event was found of the herbal medicine based on the urinalysis.

See Table 11.5 for more details.

Table 11.5 Change in urinalysis items

Test items	Results (rank number)	Group	Baseline § (mean ± SD)	*P* 1	*P* 2
pH	5.0 (1) 5.5 (2) 6.0 (3) 7.0 (4) 7.5 (5) 8.0 (6) 8.5 (7) >= 9.0 (8)	BN	4.82 ± 1.98	0.98	0.82
		PL	4.95 ± 1.86		0.17
GLU	Negative (1) 100 (2) 250 (3) 500 (4) >= 1000 (5)	BN	1.00 ± 0.00	1.00	N/A
		PL	1.00 ± 0.00		N/A
PRO	Negative (1) Trace (2) 30 (3) 100 (4) >= 300 (5)	BN	1.65 ± 0.86	0.09	0.55
		PL	1.23 ± 0.53		0.79
BLO	Negative (1) Trace-lysed (2) Trace-intact (3) Small (4) Moderate (5) Large (6)	BN	1.71 ± 0.99	0.42	0.69
		PL	1.50 ± 0.91		0.12
LEU	Negative (1) Trace (2) Small (3) Moderate (4) Large (5)	BN	1.29 ± 0.77	0.44	0.50
		PL	1.14 ± 0.47		0.68
KET	Negative (1) Trace (2) 15 (3) 40 (4) 80 (5) >= 160 (6)	BN	1.47 ± 0.80	0.17	0.07
		PL	1.14 ± 0.35		0.86

Note: § - Baseline ranking number; GLU glucose; PRO protein; BLO occult blood; LEU leukocytes; KET ketones

P 1 - Significance between two groups at baseline

P 2 - Significance within-group throughout four visits

N/A – data was not applicable for statistical analysis

11.3.3 Electrocardiogram

There was no patient during the study period found to have an abnormal ECG with clinical indications requiring them to see a cardiologist. At baseline, there were 52.9%

participants presenting with a normal ECG in the herbal medicine group and 63.6 % in the placebo group (See Table 11.6). By the end of the treatment (visit 5), two participants of the group BN who had normal ECGs at baseline showed some changes in the ECG, such as 'consider anteroseptal infarction' for one patient and 'probable left ventricular hypertrophy' for the other one, however none of these changes were considered as a change with clinical significance. In addition, both had hypertension and a history of depression and had not changed their concomitant medications throughout the trial.

In this study, the common abnormal ECGs without clinical significance included atrial fibrillation, premature complexes, bundle branch block (left or right), first degree atrioventricular block, left ventricular hypertrophy, nonspecific intraventicular conduction, PR delay, or QRST delay.

Table 11.6 Results of ECG examinations

	Group	Visit 2	Visit 5
Valid cases	BN	17	17
	PL	22	22
Cases of normal ECG (percentage)	BN	9 (52.9%)	7 (41.2%)
	PL	14 (63.6%)	16 (72.7%)
Cases of NCS ECG (percentage)	BN	8 (47.1%)	10 (58.8%)
	PL	8 (36.4%)	6 (27.3%)
Cases of change from normal to abnormal ECG of no clinical significance	BN	2	
	PL	0	
Cases of change from abnormal ECG of no clinical significance to normal ECG	BN	0	
	PL	2	

Note: NCS – no clinical significance

11.3.4 Clinical adverse events

A total of eight participants withdrew from the study before the end of the treatment (visit 5), five in the herbal medicine group (group BN) and three in the placebo group (group PL). The reasons of withdrawing from the study have been summarised in the Table 11.7.

Two patients dropped out from the study due to the amount of capsules: the daily dosage of 15 capsules caused discomfort for them, as they were taking a few medications for other chronic diseases at the same time. This reason was summarised as 'related to the trial procedure'. One patient quit the study because of an unplesant side effect, that of diarrhoea when taking the trial medicine, and it was revealed that she was randomised into the herbal medicine group. In addition, another patient withdrew from the study to undergo knee arthroscopic surgery in order to relieve the symptoms of knee OA quickly (categorised as 'related to OA' in the table). The other four participants stopped the trial owing to different personal or family issues. One of them, who was hospitalised due to a mini-stroke a few months later (after withdrawn from the clinical trial), was randomised into the placebo group.

Table 11.7 Summary of drop-out cases

Reasons of withdrawing	Group BN (n)	Group PL (n)
Personal / family issues	2	2
Related to OA	1	0
Related to the medicine/placebo	1	0
Related to the trial procedure	1	1

According to the definition of an adverse event in the study protocol (see section 11.2.1), any clinical adverse event was recorded at each visit except for the screening visit (visit 1). The summary of common clinical AEs is presented in Table 11.8.

There were 14 patients in the herbal medicine group who reported different adverse events, and 11 patients in the placebo group. The most common adverse events were the common cold and softer stools followed with diarrhoea. Participants usually took medications for their cold symptoms and did not take any action for the softer stools. However, food poisoning was blamed as the reason for diarrhoea by most of participants, although there might be some potential links with the trial or herbal medicine or placebo, as the participants were taking substances which they had not commonly used in their daily life before. Lactose intolerance might induce softer stools or diarrhoea too, given that lactose was used in the placebo capsules. Other adverse events included sore eyes, stumbling, skin bruising, tiredness, and abdominal distension (See 'others' in Table 11.8).

All participants, except for one, took various concomitant supplements or medications during the study. No side effects related to drugs interactions were found in this trial. There was only one case of a drop-out patient who was hospitalised because of a mini-stroke a few months later, which was categorised as a severe adverse event, although as mentioned, the patient was randomised to the placebo group.

Therefore, in general, softer stools could be a side effect possibly related to the herbal medicine formula, but there was no clear relationship between the trial medicine and other adverse events.

Table 11.8 Summary of common clinical adverse events

Adverse events	Group BN			Group PL		
	Times (n)	Likelihoood of a relationship to the trial medication	Action taken (n)	Times (n)	Likelihoood of a relationship to the trial medication	Action taken (n)
Cold	3	None (1) Remote (1) Possible (1)	Yes (3)	4	None (1) Remote (2) Possible (1)	Yes (4)
Cough	2	None (2)	Yes (1) No (1)	1	Remote (1)	Yes (1)
Diarrhoea	2	Remote (2)	Yes (1) No (1)	2	Possible (2)	Yes (1) No (1)
Softer stools	4	Remote (1) Possible (3)	No (4)	3	Possible (3)	No (3)
Abdominal pain	1	Remote (1)	No (1)	0	N/A	N/A
Headaches	1	Possible (1)	Yes (1)	1	Remote (1)	No (1)
Exacerbated knee pain	1	Possible (1)	No (1)	1	None (1)	Yes (1)
Frequent urination	0	N/A	N/A	1	Remote (1)	No (1)
Others	5	Remote (5)	Yes (3) No (2)	2	None (1) Remote (1)	Yes (1) No (1)

11.4 Conclusion

The herbal medicine formula appears to be safe as monitored by vital signs, laboratory tests (biochemistry, haematology) urinalysis, 12-lead electrocardiogram, concomitant medication review and adverse event reporting. The majority of vital signs, and the results of the blood and urine tests were maintained within normal range throughout the trial. Although there were some items which showed a significant change within the trial period, none fell in the abnormal range. This indicates that the application of the herbal medicine did not bring harm to participants' health. A statistical test result (*p* value) only expresses the likelihood that the result could have occurred by chance and may be different from clinical significance. There was no ECG measured at baseline or at the end of treatment which demonstrated clinical significance warranting further medical consultation or treatment. The most common adverse events during the study period were catching cold and softer stools; the latter may possibly be connected to the administration of the herbal formula. However, more studies are required to verify this finding, as a similar number of cases were also observed in the placebo group.

Chapter 12 Conclusion

12.1 Clinical treatment with Chinese herbal medicine for knee OA

Osteoarthritis (OA) is the third common cause of morbidity in Australia. Although NSAIDs and COX2 inhibitors have been widely prescribed in clinical treatment, these western drugs often cause serious side effects. Many patients with OA are using different forms of complementary and alternative medicine (CAM), including glucosamine, chondroitin and herbal medicines. The evidence relating to the efficacy of various forms of CAM is variable; it is more convincing for some CAM products such as glucosamine and less convincing for others. Chinese medicine (CM) is an increasing popular form of CAM used in the treatment of OA. The treatment modalities include acupuncture and Chinese herbal medicine (CHM). A limited number of acupuncture studies that are of good quality suggest that acupuncture is efficacious in reducing knee pain. There have also been many efficacy studies of CHM treatment of OA which have claimed positive results, however, the quality of those trials was poor. This clinical study was the first randomised, double-blind, placebo controlled clinical trial conducted in Australia to investigate the efficacy of a Chinese herbal medicinal formula in alleviating symptoms of knee OA.

12.1.1 Study quality

According to the literature review (Chapter 5), the methodological problems associated with the majority of previous CHM studies include not using reliable diagnostic criteria, lack of information on randomisation and blinding procedures, absence of a placebo comparison and even analysing with inappropriate statistical methods. Therefore, this trial was conducted based on the CONSORT (Consolidated Standards of Reporting Trials) Guidelines, a checklist regarding the quality associated with planning, conducting and interpretation of clinical trials (See Appendix 1), in order that the study was of a rigorous standard.

This study has clearly stated its scientific background, rationale and methods including randomisation and allocation concealment, and blinding procedures.

12.1.2 Study design and Chinese medicine

According to the CONSORT checklist for trials of herbal interventions (see Appendix 1), interventions of herbal medicine require consideration of traditional theories and concepts which should be reflected in the participant inclusion criteria. In addition, the precise details of the herbal interventions, such as herbal medicinal names, characteristics of the herbal product, dosage regimen and quantitative description should be included.

However, Chinese medicine (CM) diagnostic criteria of knee OA were not used in the participant recruitment in this study though the traditional CM indications and concepts underpinned much of the study. There were three reasons.

First of all, there was no disease named OA in traditional Chinese medicine. This is a biomedically defined disease adopted into modern CM. According to traditional theory, it is generally believed that OA should be categorised as Bi Syndrome, specifically Bi syndrome of Bone. But there is no one-to-one corresponding relationship between OA and Bi syndrome. This has led to the current diagnostic criteria of OA in the two official clinical guidelines of the People's Republic of China being based on western medical diagnostic criteria, as no CM symptoms or signs that are specific to OA only. (China State Administration of Traditional Chinese Medicine, 1994, China State Bureau of Technical Supervision, 1997)

Secondly, the theory that OA is a combination of Wei Syndrome and Bi Syndrome is a relatively new theory. This theory is still hypothetical even though there are some clinical and animal studies to support this notion.(Cao et al., 2004b, Shi et al., 1994, Shen et al., 1995, Wang et al., 1998) There are no valid, existing diagnostic criteria relating to the combination of Wei Syndrome and Bi Syndrome. Therefore, in investigating the efficacy a formula that is developed on the basis of this new theory, the theory was in fact being tested out. The assumption was that patients with OA of the knee would demonstrate characteristics of this combined Syndrome. This is similar to the traditional approach to summarising all kinds of rheumatological diseases under the category of Bi Syndrome, on the basis (assumption) that they have characteristics of Bi Syndrome. Therefore, I have

made an assumption: that all of the OA population are eligible for the treatment based on this theory of a combined Syndrome. In modern CM, there is a trend to look for a general or common pathogenesis for particular 'modern' (that is, biomedically-defined) diseases. This method has been applied in clinical research and the findings have also successfully been adopted into CM theory. This is called 'integrative medicine' in China.(Liu et al., 2010) For example, the therapeutic effect of the CM treatment principle of 'invigorating Blood circulation and eliminating Blood stasis' is a feature of treatments for coronary heart disease (CHD), and these treatments are based on a theoretical hypothesis that CHD is due to the pathologic changes associated with 'Blood stagnation', where the CM Syndrome is the 'Syndrome of Blood Stagnation'. Nowadays, this Syndrome has been generally accepted as being characteristic of CHD and treatment is aimed mainly at this Syndrome.

Thirdly, there is still some question about the reliability of the CM diagnostic system. In addition, there is no objective evidence of the potential diagnostic subcategories of OA, despite the fact that modern texts have listed several. Thus, in the absence of evidence that CM diagnostic variables are reliable, we did not use CM inclusion criteria to recruit the participants. A sub-study of the efficacy trial was conducted to test the reliability of the CM diagnostic system, in order to ascertain if CM diagnostic variables could be used as outcome variables and incorporated into the main study. The results of the inter-rater reliability study did not show reliable CM Syndrome diagnoses of OA and the majority of CM diagnostic methods also were not reliable. The inclusion of CM diagnostic endpoints has not been justified, and therefore the CM inclusion criteria were not incorporated into the study design.

In the end, although the study design and protocol were rigorous, there were less eligible participants than the required numbers based on the sample size calculation. This was due to the limited budget and time for the Ph.D study. This is likely to have influenced the study findings, particularly in relation to the statistical analyses and the interpretation of results.

12.1.3 Efficacy and safety of the clinical treatment of Chinese herbal medicine for OA

Evaluation of the clinical efficacy was assessed by the WOMAC index, SF-36, Patient Global Assessment and Physician Global Assessment in this study. There were 47 patients randomised into the two groups (herbal medicine group or placebo group).

No significant difference was found between the groups in their mean daily physical exercise and nutrition intake during the study period, thus change in exercise or nutrition were not confounding factors. There was insufficient data for the Physician Global Assessment leading to less useful convincing evidence of a rheumatologist's perspective on the clinical efficacy of this herbal medicine treatment for OA.

The SF-36 assessment indicated that the physical health of participants did not significantly change throughout the trial. Patients in the placebo group showed a significant improvement in their mental health at the end of the treatment, which was not found in the herbal medicine group. However this kind improvement disappeared during the follow-up period. The conclusion based on the SF-36 assessment was that the health status of all of participants was stable in this trial. This also corresponded with the results of the Patient Global Assessment - that participants did not experience any significant change in term of the general impact of knee OA.

The WOMAC index indicated that OA symptoms significantly improved at the end of the herbal treatment, with reduced scores in knee pain, stiffness, and physical activity and total score. The scores did not rebound significantly during the follow-up period suggesting the effectiveness of herbal medicine was maintained, at least for one month. This compares favourably compared to the placebo group. Although the score of pain and physical activity and total score were also reduced significantly at visit 5, this disappeared quickly in the follow-up period in the placebo group. Further, the stiffness score of the placebo group failed to show any significant change throughout the trial. In addition, the improvement in pain and physical activity in the placebo group disappeared quickly in the follow-up period. Although there was not any statistical significance found between the two groups in terms of pain, stiffness and physical activity or total score, the

study findings provide some limited support for the contention that the study CHM formula can improve symptoms of stiffness for knee OA, above a potential placebo effect, given that the study did not recruit as many participants as required for 80% power. In addition, a significant difference between the two groups in the WOMAC score may have been found if the treatment time was longer than three months, considering the fact that the reduced WOMAC score did not rebound significantly in the CHM group during the follow-up period. It is likely that CM is a kind of slow- acting medicine. OA is a chronic disease and so it may be that a longer time period would be needed for treatment.

In this study no severe side effects occurred. Safety was monitored by vital signs, laboratory tests (biochemistry, haematology, and urinalysis), 12-lead electrocardiogram, concomitant medication review and adverse event reporting. Vital signs and the results of blood and urine tests stayed within normal ranges throughout the trial, and no participant demonstrated an abnormal ECG which required further medical consultation or treatment. The most common adverse event was softer stools which were found in both groups. This could be a possible side effect of the herbal formula, but more studies are required to verify this.

12.1.4 Application of the theory of a combined Syndrome for OA

The study formula was developed based on a theory that treats OA as a combined Syndrome of Wei Syndrome and Bi Syndrome. If efficacy of the formula had been demonstrated relative to the placebo, this would provide some scientific evidence in support of this theory.

The original study formula (composed of four herbs) has been strengthened by the addition of two herbs with the function of nourishing the Liver. Deficiency of the Liver is the fundamental basis of Wei Syndrome. The previous study on which the current formula was developed did not find any significant reduction in the WOMAC scores for pain, stiffness and physical activity compared with another CHM formula, but showed a significant improvement in pain, stiffness and physical activity within the study group in a four week treatment period, particularly during the period between week 2 and week 4. Our trial demonstrated a significant improvement in relief of stiffness of the knee joint in

the treatment group, and this effect could be due to the herbal medicine, that is, not just a placebo effect. Knee stiffness, in CM, is usually explained as being due to a lack of Blood that has the action of nourishing and moistening the sinews around the knee joint. This new theory is a reasonable explanation of the pathogenesis of OA. However, more studies of long-term and large scale are required to verify this.

12.2 Reliability of the Chinese medicine diagnostic system

The Chinese medicine diagnostic system includes three main components: diagnostic methods, the Eight Guiding Principles and Syndrome Diagnosis, which could be interpreted as data collection, data categorisation and data analysis. Syndrome diagnosis is the ultimate goal. Some studies have shown a low reliability in Syndrome diagnosis amongst different diseases (see section 6.4 in Chapter 6). This raises a question of whether it is due to the unreliable data collection or data categorisation, or whether in some cases, an inappropriate theory has applied to a particular disease. Therefore, this study broke the diagnostic process of knee OA into a few steps- collecting of the data (the basics) then organisation of this data according to a basic theory (Eight Guiding Principles) then a more complex theory (Zang-Fu), in order to find out the reliability at each level.

12.2.1 Reliability of clinical diagnostic variables

This was the first reliability study to investigate all four CM diagnostic methods conducted in a CM examination (Inquiry, Inspection, Auscultation and Palpation). As a relatively new research field in CM, there have not been any other reliability studies to investigate the four CM diagnostic methods as an entirety. The integration of all diagnostic methods has actually always been emphasised as one of three main principles in traditional CM Diagnostics, which is the ‘correlation of all four examinations’, the other two being ‘taking the inside changes and outside factors into consideration’ and ‘tracing causes of the disease through Syndrome Differentiation’ (Deng et al., 1984). This study has therefore made an important contribution.

In this study, a relatively good level of agreement for most Inquiry variables was found. Almost 50% of the Inquiry endpoints reached a ‘substantial’ to ‘almost perfect’ level of

agreement (according to the interpretation of the Kappa coefficient analysis). But these questions mainly asked about the presence or absence of a certain symptom, a yes/no answer, which makes it relatively easy to achieve agreement between different raters. In addition a standardised form was used in this study and choices of responses were fixed, so this setting might also contribute to a reasonably high level of agreement on Inquiry variables. However, there were 23 questions which could not be analysed by the Kappa coefficient due to the limitations of the Kappa analysis. Therefore, caution should be taken in judging the real reliability of the Inquiry method.

Eight aspects of the body were used as Inspection variables, including appearance of the tongue. A 'slight' to 'fair' level of agreement was found for the majority of Inspection variables. There were only two variables which had 'moderate' agreement between two practitioners: observation of the amount of hair and the type of body frame. Only one question relating to the temperature of the hands achieved 'substantial' agreement. Given the form used fixed response choices, the findings indicate a relatively low level of agreement overall for Inspection variables. The low agreement on Inspection variables found in this study suggests that this aspect of the CM examination is quite subjective, and that clear definitions of those characteristics in CM are needed. The level of agreement between two practitioners on the strength of voice and character of breathing sounds was reasonably high. There were only two Auscultation variables used in this study. More studies are needed to establish the reproducibility of Auscultation variables in CM. Pulse characteristics were used as the main Palpation variables in this study. Results indicated 'poor' agreement for one aspect, 'slight' agreement for four aspects, and 'fair' for another item of pulse. A low overall agreement on pulse characteristics was found in this study. These results are understandable as pulse diagnosis is the most difficult part of the art of CM diagnosis, requiring extensive clinical experience to master.

In general, there was a relatively good level of agreement for Inquiry and Auscultation variables, and a low level of agreement for Inspection and Palpation variables. Based on the results, it was inappropriate to use CM diagnostic variables as diagnostic endpoints in the main efficacy study, given that reliability had not been demonstrated.

Future work investigating the reliability of CM diagnostic variables should include the development of a CM assessment form that is very specific to the disorder under investigation. Insufficient specific questions or diagnostic variables may reduce the reliability of CM diagnosis. In the current CM assessment form, although there are some questions regarding OA, in hindsight they might not represent the full picture of knee OA. Some techniques could be helpful to build up a more efficient assessment form. For example, standardised tongue colour charts could increase the opportunity to reach consensus on the definitions of tongue colour. Tongue diagnosis is a very useful diagnostic index in CM, and was used as the most important method leading to the final Syndrome Diagnosis for one practitioner in this study.

12.2.2 Reliability of the Eight Guiding Principles

The Eight Guiding Principles is the foundation for all the other methods of Syndrome Differentiation in CM diagnosis. The results from this study showed agreement on the Interior/Exterior pair was 97.5% and the majority of participants were identified as 'Deficiency' patterns. This is consistent with CM theory that suggests that knee OA is mainly caused by weakness of the person's constitution. However, Kappa values for Hot/Cold pair and Excess/Deficiency pair indicated there was 'slight' and 'poor' agreement between two practitioners. This might simply indicate the complexity of the characteristics of OA, a chronic disease which is a mixture of deficient causes and excess presentations (e.g. pain). As for the Yin/Yang pair, one practitioner categorised all of participants as Yin, and the other practitioner rated 67.5% of all participants as Yin.

These results support the argument that OA of knee is more likely to be an internal disease with manifestations of deficient symptoms (such as the weakness of knee, impaired movements and pain or stiffness in the knees). These findings could be thought as providing some 'empirical' evidence to support the notion of pathogenesis of OA according to CM theories. However, a conclusion relating to the reliability of the Eight Guiding Principles in clinical practice cannot be gained from this OA study only. More studies should be conducted in different medical conditions.

12.2.3 Reliability of Syndrome diagnosis based on Zang-Fu theory

In this study, all of the multi-CM Syndrome diagnoses were separated into individual CM Syndrome components based on Zang Fu Theory. Two levels of agreement were used: exact/strict and partial. In addition, an open-ended Syndrome diagnosis design was adopted in this study in order to investigate the potential spectrum of possible OA Syndromes. This design is more likely to result in a lower level of agreement than if a fixed list of Syndromes was provided.

The average number of CM Syndromes diagnosed for the two practitioners was 2.0 and 2.9 respectively, and the level of strict agreement was 0% and partial agreement was only 50.0%. Highest agreement was found on the single Syndrome of Spleen Qi Deficiency (23.1%), followed by Kidney Yin Deficiency (12.8%). In addition, the most common involved Meridians were the Kidney Meridian (30.0% agreement), Liver Meridian (25.0% agreement) and Spleen Meridian (15.0% agreement). These findings are in support of the CM theory tested in this herbal medicine trial, which is that OA is due to a lack of Blood nourishing the knee joints and Deficiency of the Liver and Kidney. In addition, since the Spleen is responsible for generation of Blood via transformation from food, the finding of the Spleen meridian being involved is consistent with this theory. Although Syndrome diagnosis is the core of CM Diagnosis, there has been only one other study which investigated the reliability of Syndrome diagnosis according to both the Eight Guiding Principles and Zang-Fu Theory (O'Brien et al., 2009a). This study is a therefore an important contribution to development of this knowledge.

In general, a low level of agreement and variable Syndrome diagnoses of knee OA according to Zang-Fu Theory were found in this study. As a new disease adopted into CM, it is possible that Zang-Fu theory might not be the best theory to characterise OA. An average of 2.5 single Syndromes per practitioner based on Zang-Fu Theory was found in this study. This could simply indicate the complexity of OA. It also poses an important new question for future study: whether OA should be categorised under a general Syndrome diagnosis (like Bi Syndrome, or a combination of Bi Syndrome and Wei Syndrome), or differentiated to single Syndromes based on Zang-Fu Theory, or even based on another theory (e.g. Meridian Theory).

This also raises questions about the applicability of Zang-Fu Theory to biomedically-defined diseases. It highlights an existing debate in CM about how to integrate Syndrome-orientated diagnosis with disease-oriented diagnosis in CM, especially for these 'new' (biomedically-defined) diseases that were not specified as distinct entities in classic Chinese medical texts. For some diseases, it may be appropriate that disease diagnosis is the fundamental target of treatment if a common underlying pathogenesis is found. For example, a common underlying pathogenesis (Syndrome of Blood stasis) has been found in CHD, therefore, the clinical treatments of CHD concentrate on 'invigorating Blood circulation and eliminating Blood stasis' instead of Syndrome Differentiation according to Zang-Fu Theory, which may cause confusion in this particular disease. For other diseases, CM Syndrome diagnosis remains the guiding treatment principle. For example, the different stages of lymphoma development cannot be categorised by a single Syndrome, thus Syndrome diagnosis is necessary in its CM treatment. There is also a concern about the pivotal role of Syndrome diagnosis in CM. Syndrome diagnosis only became central to CM Diagnostics since the Qing Dynasty onwards and this importance was strengthened in the mid-twentieth century (Scheid, 2002). But it may not be appropriate for some diseases. In addition, in some ancient literature of CM only the disease diagnosis was actually used. For example, a Master of traditional CM, Dr. Zhang Zhongjing only used disease names to categorise different clinical manifestations in his classic text, the *Shang Han Lun*. (Scheid, 2002) More studies should be conducted to ascertain which disorders or conditions Syndrome Diagnosis can appropriately be applied to.

There was only one other previous study that comprehensively investigated the reliability of CM diagnostic system excluding the Inquiry component. Therefore, the current study was the first study to give a full picture of the reliability of the CM diagnostic system. In addition, CM is a popular modality used in the treatment for rheumatological disorders, however, there have been very few studies which have tested the reliability of CM diagnosis reliability in these diseases. This study was the first inter-rater reliability study in OA. Considering the fact that the reliability study of CM diagnostic system is still a new field in CM, this study has contributed to a growing body of knowledge about CM Diagnostics, particularly for OA.

The study also found there was variation between practitioners in terms of emphasis on particular techniques used for making a diagnosis of OA. This result corresponds to a few previous studies which also found that the CM practitioners emphasised on different diagnostic techniques in their practice (see Section 9.7.3 of Chapter 9). Although the reasons for these tendencies amongst CM practitioners are still unknown, this study has provided materials which may be of use in future research and for CM education.

Based on the findings of this reliability study of CM diagnosis in knee OA, there was a relatively low level of agreement in the first step of the diagnosis process, the four diagnostic methods (data collection). There was a variable level of agreement in Syndrome diagnosis according to the Eight Guiding Principles (data categorisation). The finding that there was a low level of agreement for Syndrome diagnosis according to Zang-Fu theory (data analysis) is therefore not surprising. In addition, no CM diagnostic endpoints demonstrated sufficient reliability to justify inclusion in the clinical efficacy trial.

12.3 Limitations of and perspectives on the efficacy study and the reliability study

This was a pilot study of a Chinese herbal medicine formula and there were some limitations which may have impaired its results. First of all, the numbers of participants recruited were less than required resulting in a lower power to detect a change in the primary outcome variable. Secondly, the actual dose of the herbal medicine capsule was less than the traditional dosages of equivalent raw herbs which may have resulted in a weaker therapeutic effect. A larger scale study over a longer time period is needed in order to investigate the real efficacy of this Chinese herbal medicine formula.

An important finding of this clinical trial was that the Chinese herbal formula could significantly ease stiffness of the knee (which was not seen in the placebo group). It is suggested that the stiffness score of WOMAC could be a sensitive and valuable index for future studies of the efficacy of Chinese herbal medicines designed for the treatment of OA based on the theory of nourishing the Liver.

In the reliability study of the CM diagnostic system, on reflection the current CM assessment form may not have been sensitive enough to detect the real conditions of

patients with knee OA. A finding of low reliability of CM diagnosis in this one OA study results is not sufficient to reach a conclusion that the entire CM diagnosis system is unreliable. Future studies need to be conducted in order to try to characterise the explicit CM symptoms and signs of OA of the knee and to establish a more efficient assessment form. Deficiency of the Kidney and Deficiency of the Spleen were the most common Syndromes found amongst this study population with knee OA. However, as the first study on the reliability of Syndrome Diagnosis on knee OA, more comparison studies should be done in order to establish the (reliable) main CM Syndrome or an actual range of Syndromes of knee OA. Once this has been established and verified, the particular Syndrome(s) could be used as a guide to develop a more specific CM assessment tool for OA and rheumatological diseases, and validate it for use.

In addition, prior training of diagnostic assessment skills amongst assessors may be useful for future studies, which could minimise or reduce potentially interfering factors such as difference in personal clinical experiences or misunderstanding the definitions of assessment variables, particularly for chronic diseases like OA which usually have more complex clinical presentations.

There is a need to build up a range of reliable CM diagnostic variables for future CM randomised clinical trials. This is because these variables are actually clinical endpoints used in daily clinical practice to guide treatment and they are more meaningful to CM practitioners to ascertain the effectiveness of herbal medicines. Current CM clinical trials usually adopt western medical diagnostic endpoints as the assessment tools, which was also seen in this study (like the WOMAC index). This is mainly because the reliability and validity of CM variables have not been established. The majority of diagnostic variables and the CM Syndromes (according to Zang-Fu Theory) were not found to be reliable in this study. However, for some diseases ‘new’ to CM like OA, Zang-Fu Theory may not be the best theory to diagnose its Syndromes, though it is the predominant theory in CM. In CM, there are also other theories of Syndrome Diagnosis, such as Meridian Theory and the Theory of Qi, Blood and Body Fluids. Future research could investigate the applicability of other theories to OA. Once the reliable variables and CM Syndromes have been established, these endpoints could be used as inclusion or exclusion criteria

integrated into the study design and used as outcome indices in addition to western medicine variables. Future OA research directions could include the investigation of other CM Syndrome diagnosis theories, such as the theory of ‘Syndrome Diagnosis according to the Meridians’.

This study was a small pilot study of the Bai Niu capsule. Although a trend of a therapeutic effect was demonstrated in the study results, a larger scale study that is appropriately powered would need to be conducted in order to answer the question of whether it is efficacious or not.

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APPENDIX 1 CONSORT Checklist of items for studies of herbal treatments

Section / Topic	Item	CONSORT Description
Title and Abstract	1	How participants were allocated to intervention (for example: "random allocation", "randomised", or "randomly assigned"). Either the title or abstract, or both should state the herbal medicinal product's Latin binomial, the part of the plant used, and the type of preparation
Introduction		
Background	2	Scientific background and explanation of rationale Including a brief statement of reasons for the trial with reference to the specific herbal medicinal product being tested and, if applicable, whether new or traditional indications are being investigated
Methods		
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected If a traditional indication is being tested, a description of how the traditional theories and concepts were maintained. For example, participant inclusion criteria should reflect the theories and concepts underlying the traditional indication.
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered
	4A	Herbal medicinal product name 1. The Latin binomial name together with botanical authority and family name for each herbal ingredient; common name (s) should also be included. 2. The proprietary product name (i.e. brand name) or the extract name (e.g. EGb-761) and the name of the manufacturer of the product. 3. Whether the product used is authorised (licensed, registered) in the country in which the study was conducted.
	4B	Characteristics of the herbal product 1. The part(s) of plant used to produce the product or extract. 2. The type of product used [e.g. raw (fresh or dry), extract. 3. The type and concentration of extraction solvent used (e.g. how done and by whom) and the lot number of the raw material. State if a voucher specimen (i.e. retention sample) was retained and, if so, where it is kept or deposited, and the reference number.
	4C	Dosage regimen and quantitative description 1. The dosage of the product, the duration of administration, and how these were determined. 2. The content (e.g., as weight; concentration; may be given as range where appropriate) of all quantified herbal product constituents, both native and added, per dosage unit form. Added materials, such as blinders, fillers, and other excipients (e.g. 17% maltodextrin, 3% silicon, dioxide per capsule) should also be

		listed. 3. For standardised products, the quantity of active/marker constituents per dosage unit form.
	4D	Qualitative testing 1. Product's chemical fingerprint and methods used (equipment and chemical reference standards) and who performed it (e.g., the name of the labouratory used). Whether or not a sample of the product (i.e., retention sample) was retained and if so, where it is kept or deposited. 2. Description of any special testing/purity testing (e.g., heavy metal or other contaminant testing) undertaken. Which unwanted components were removed and how (i.e., methods). 3. Standardisation: what to (e.g., which chemical component(s)of the product) and how (e.g., chemical processes or biological/functional measures of activity).
	4E	The rationale for the type of control/placebo used.
	4F	A description of the practitioners (e.g., training and practice experience) that are a part of the intervention.
Objectives	5	Specific objectives and hypotheses
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable; any methods used to enhance the quality of measurements (e.g. multiple observations, training of assessors) Outcome measures should reflect the intervention and indications tested considering, where applicable; underlying theories and concepts.
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analysis and stopping rules.
Randomisation sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g. blocking, stratification).
Allocation concealment	9	Method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.
Statistical methods	12	Statistical methods used to compare groups to primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.
Results		
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended)-specially, for each group, report the numbers of participants randomly assigned, receiving intended treatment,

		completing the study protocol, and analysed for the primary outcome; describe protocol deviations from study as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up
Baseline data	15	Baseline demographic and clinical characteristics of each group Including concomitant medication, herbal, and complementary medicine use.
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether analysis was by "intention-to-treat"; state the results in absolute numbers when feasible (e.g. 10/20, not 50%)
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g. 95% confidence interval)
Ancillary analysis	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory
Adverse events	19	All important adverse events or side effects in each intervention group
Discussion		
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes Interpretation of the results in light of the product and dosage regimen used.
Generalisability	21	Generalisability (external validity) of the trial findings Where possible, discuss how the herbal product and dosage regimen used relate to what is used in self-care and/or practice.
Overall evidence	22	General interpretation of the results in the context of current evidence. Discussion of the trial results in relation to trials of other available products.

APPENDIX 2 CONSORT Checklist of items for studies of nonpharmacologic treatments

Section / Topic	Item	CONSORT Description
Title and Abstract	1	How participants were allocated to intervention (for example: "random allocation", "randomised", or "randomly assigned"). In the abstract, description of the experimental treatment, comparator, care providers, centres, and blinding status.
Introduction		
Background	2	Scientific background and explanation of rationale
Methods		
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected When applicable, eligibility criteria for centres and those performing the interventions
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered Precise details of both the experimental treatment and comparator
	4A	Description of the different components of the interventions and, when applicable, descriptions of the procedure for tailoring the interventions to individual participants
	4B	Details of how the interventions were standardised
	4C	Details of how adherence of care providers with the protocol was assessed or enhanced
Objectives	5	Specific objectives and hypotheses
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable; any methods used to enhance the quality of measurements (e.g. multiple observations, training of assessors)
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analysis and stopping rules When applicable, details of whether and how the clustering by care providers or centres was addressed
Randomisation sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g. blocking, stratification) When applicable, how care providers were allocated to each trial group
Allocation concealment	9	Method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups
Blinding (masking)	11A	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment

		Whether or not those administering co-interventions were blinded to group assignment
	11B	If blinded, method of blinding and description of the similarity of interventions
Statistical methods	12	Statistical methods used to compare groups to primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses When applicable, details of whether and how the clustering by care providers or centres was addressed
Results		
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended)-specially, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome; describe protocol deviations from study as planned, together with reasons The number of care providers or centres performing the intervention in each group and the number of patients treated by each care provider or in each centre
Implementation of intervention	New item	Details of the experimental treatment and comparator as they were implemented
Recruitment	14	Dates defining the periods of recruitment and follow-up
Baseline data	15	Baseline demographic and clinical characteristics of each group When applicable, a description of care providers (care volume, qualification, expertise, etc.) and centres (volume) in each group
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether analysis was by "intention-to-treat"; state the results in absolute numbers when feasible (e.g. 10/20, not 50%)
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g. 95% confidence interval)
Ancillary analysis	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory
Adverse events	19	All important adverse events or side effects in each intervention group
Discussion		
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centres in each group
Generalisability	21	Generalisability (external validity) of the trial findings according

		to the intervention, comparators, patients, and care providers and centres involved in the trial
Overall evidence	22	General interpretation of the results in the context of current evidence

APPENDIX 3

WOMAC OSTEOARTHRITIS INDEX VERSION VA3.1

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions will be asked in the following format. You should give your answers by putting an " X " on the horizontal line.

EXAMPLES:

1. If you put your " X " at the left of the line as shown below, then you are indicating that you have **no** pain.

2. If you put your " X " at the right end of the line as shown below, then you are indicating that your pain is **extreme.**

3. Please note:
   a) that the further to the right you place your " X " the more pain you are experiencing.
   b) that the further to the left you place your " X " the less pain you are experiencing.
   c) **please do not place your " X " past the end of the line.**

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.

Think about your _____ (study joint) when answering the questionnaire. Indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your _____ (study joint).

Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.

Australia - V4

WOMAC VA3.1 QUESTIONNAIRE WOMA

Section A

PAIN

Think about the pain you felt in your _____ (study joint) due to your arthritis during the last 48 hours.

(Please mark your answers with an "✗" on the horizontal line.)

QUESTION: **How much pain do you have?**

1. Walking on a flat, even surface.

No Pain ——— Extreme Pain

2. Going up or down stairs.

No Pain ——— Extreme Pain

3. At night while in bed, i.e., pain that disturbs your sleep.

No Pain ——— Extreme Pain

4. Sitting or lying awake in bed.

No Pain ——— Extreme Pain

5. Standing upright (but not moving).

No Pain ——— Extreme Pain

Study Coordinator Use Only	
PAIN1	____
PAIN2	____
PAIN3	____
PAIN4	____
PAIN5	____

Australia - V4

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your_____ (study joint) due to your arthritis during the last 48 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

(Please mark your answers with an " X " on the horizontal line.)

6. How severe is your stiffness after first awakening in the morning?

No Stiffness — Extreme Stiffness

7. How severe is your stiffness immediately after sitting, lying or resting later in the day?

No Stiffness — Extreme Stiffness

Study Coordinator Use Only

STIFF6 _____

STIFF7 _____

Australia - V4

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself.** (Please mark your answers with an " X " on the horizontal line.)

QUESTION: **What degree of difficulty do you have?**

		Study Coordinator Use Only
8. Going down stairs.	No Difficulty — Extreme Difficulty	PFTN8 _____
9. Going up stairs.	No Difficulty — Extreme Difficulty	PFTN9 _____
10. Standing up after sitting.	No Difficulty — Extreme Difficulty	PFTN10 _____
11. Standing (in one position).	No Difficulty — Extreme Difficulty	PFTN11 _____
12. Bending to the floor, i.e., to pick something up.	No Difficulty — Extreme Difficulty	PFTN12 _____
13. Walking on a flat, even surface.	No Difficulty — Extreme Difficulty	PFTN13 _____

Australia - V4

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself.** (Please mark your answers with an " X " on the horizontal line.)

QUESTION: **What degree of difficulty do you have?**

		Study Coordinator Use Only
14. Getting in or out of a car, or getting on or off a bus.	No Difficulty — Extreme Difficulty	PFTN14 _____
15. Going shopping.	No Difficulty — Extreme Difficulty	PFTN15 _____
16. Putting on your socks or stockings.	No Difficulty — Extreme Difficulty	PFTN16 _____
17. Getting out of bed.	No Difficulty — Extreme Difficulty	PFTN17 _____
18. Taking off your socks or stockings.	No Difficulty — Extreme Difficulty	PFTN18 _____
19. Lying and turning in bed.	No Difficulty — Extreme Difficulty	PFTN19 _____

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and to look after yourself.** (Please mark your answers with an " X " on the horizontal line.)

QUESTION: What degree of difficulty do you have?	Study Coordinator Use Only
20. Getting in or out of the bath. No Difficulty ——— Extreme Difficulty	PFTN20 ____
21. Sitting. No Difficulty ——— Extreme Difficulty	PFTN21 ____
22. Getting on or off the toilet. No Difficulty ——— Extreme Difficulty	PFTN22 ____
23. Performing heavy domestic duties. No Difficulty ——— Extreme Difficulty	PFTN23 ____
24. Performing light domestic duties. No Difficulty ——— Extreme Difficulty	PFTN24 ____

Australia - V4

APPENDIX 4 Physician Global Assessment

Patient's Information:

First Name:	**Surname:**	□ **Male**
Date of Birth (dd/mm/yyyy)	**Participant Number:**	**Gender:** □ **Female**

Date of Visit:

Physician Name: **Physician Signature:**

Question 1

Considering all the ways OA affects your patient, how would you rate him/her condition today by marking a '×' in one box below?

□ 0= very well □ 1= well □ 2= fair □ 3= poor □ 4= very poor

The question below will be answered at the end of study only.

Question 2

Considering all the ways OA affects your patient, how would you rate him/her condition now compared with the beginning of the study with the therapeutic effect of the study medication?

□ 0= no response, absence of drug effect	□ 1= poor, minor response, unacceptable	□ 2= fair, definite response but could be better	□ 3= good, good response, but less than the best possible anticipated response	□ 4= excellent, the best possible anticipated response considering the severity and stage of the disease

APPENDIX 5 Patient Global Assessment

First Name:	**Surname:**	□ **Male**
Date of Birth (dd/mm/yyyy)	**Participant Number:**	**Gender:** □ **Female**
Date of Visit:		

Instruction:

You should give your answer by putting an "X" on the horizontal line, Please **do not** place your "X" past the end of the line.

Question:

Considering all the ways your osteoarthritis affects you, how would you rate your condition today?

Patient's Signature:

APPENDIX 6 SF-36

Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3 The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a kilometre	☐ 1	☐ 2	☐ 3
h Walking several hundred metres	☐ 1	☐ 2	☐ 3
i Walking one hundred metres	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

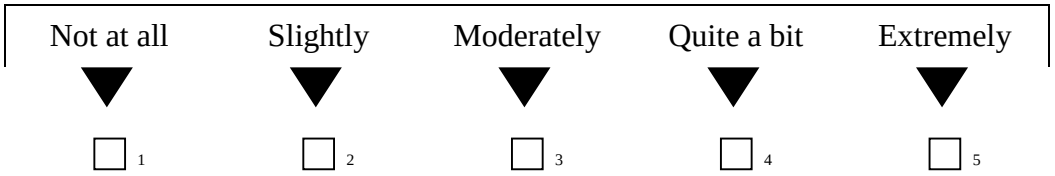
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

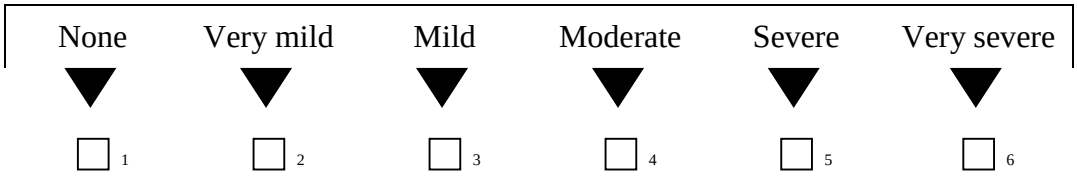
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

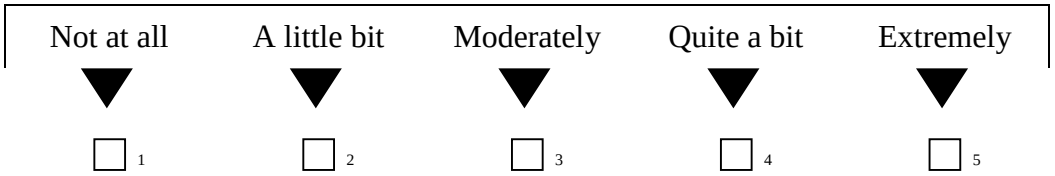
6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?



7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?



8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

APPENDIX 7 Baecke Physical Activity Questionnaires

Participant Name:_____

Date:_____

Instructions

This questionnaire is to be completed by you. It should take about 10 minutes to complete.

Please tick the most appropriate answer, or complete your response in the spaces given.

If you don't work or study, respond "nil" in questions 1 and leave questions 2-8 blank. If you work and study, respond to questions 2-8 only for your work.

In question 9, "sport" includes running, gym, swimming aswell as sports such as golf, tennis, cricket and football. If you go walking as a form of exercise, put it down here as a sport. If you participate in more than 2 "sports", please respond for the 2 sports you participate most in.

Questionnaire

1. What is your main occupation?
❑ (Please specify) ❑ nil

2. At work I sit
❑ never ❑ seldom ❑ sometimes ❑ often ❑ always

3. At work I stand
❑ never ❑ seldom ❑ sometimes ❑ often ❑ always

4. At work I walk
❑ never ❑ seldom ❑ sometimes ❑ often ❑ always

5. At work I lift heavy loads
❑ never ❑ seldom ❑ sometimes ❑ often ❑ always

6.After working I am tired
❑ very often ❑ often ❑ sometimes ❑ seldom ❑ never

7. At work I sweat
❑ very often ❑ often ❑ sometimes ❑ seldom ❑ never

8. In comparison with others my own age I think my work is physically
❑ much heavier ❑ heavier ❑ as heavy ❑ lighter ❑ much lighter

9. Do you play sport?
❑ Yes ❑ no

9a.If yes:
9a1. which sports do you play most frequently?
❑ (Please specify)

9a2. how many hours per week?
❑ <1 ❑ 1-2 ❑ 2-3 ❑ 3-4 ❑ >4

9a3. how many months per year?
❑ <1 ❑ 1-3 ❑ 4-6 ❑ 7-9 ❑ >9

9b. if you play a second sport:
9b1. which sports do you play most frequently?
❑ (Please specify) ❑ nil

9b2. how many hours per week?
❑ <1 ❑ 1-2 ❑ 2-3 ❑ 3-4 ❑ >4

9b3. how many months per year?
❑ <1 ❑ 1-3 ❑ 4-6 ❑ 7-9 ❑ >9

10. In comparison with others my own age I think my physical activity during leisure time is: ❑ much more ❑ more ❑ the same ❑ less ❑ much less

11. During leisure time I sweat
❑ very often ❑ often ❑ sometimes ❑ selfdom ❑ never

12. During leisure time I play sport
❑ never ❑ seldom ❑ sometimes ❑ often ❑ very often

13. During leisure time I watch television
❑ never ❑ seldom ❑ sometimes ❑ often ❑ very often

14. During leisure time I walk
❑ never ❑ seldom ❑ sometimes ❑ often ❑ very often
15. During leisure time I cycle
❑ never ❑ seldom ❑ sometimes ❑ often ❑ very often

16. How many minutes per day do you walk and/or cycle per day to and from work, school, and shopping?
❑ <5 ❑ 5-15 ❑ 15-30 ❑ 30-45 ❑ >45

APPENDIX 8

Chinese Medicine Assessment Form

Name of Chinese Medicine Practictioner (Please Print): _____

Signature : _____

Subject initials: __ __ __ **Subject Number:** __ __ __

Date of Visit: **Visit 2** ❑ **Visit 5** ❑

A. INQUIRY

A1) FEVER, CHILLS AND BODY TEMPERATURE

A1a) Do you experience chills i.e. a shivering feeling of cold that is relieved by warm clothes or heat?

❑ Yes ❑ No

A1a1).If yes, do you feel:

❑ Slight chills ❑ Moderate chills ❑ Strong chills

A1b) Do you generally feel cold that is not relieved by warm clothes or heat?

❑ Yes ❑ No

A1b1).If yes, are you:

❑ Slightly cold ❑ Moderately cold ❑ Very cold

A1c) Do you experience cold hands and feet?

❑ Yes ❑ No

A1c1).If yes, are your hands and feet:

❑ Slightly cold ❑ Moderately cold ❑ Very cold

A1d) Are you sensitive to cold?

❑ Yes ❑ No

A1d1). If yes: Are you:

❑ Slightly sensitive to cold ❑ Moderately sensitive to cold ❑ Very sensitive to cold

A1d2) Additional information: _____

_____

A1e) Are you particularly sensitive to heat (that is, you have an aversion to heat)?

❑ Yes ❑ No

A1e1). If yes: Are you:

❑ Slightly sensitive to heat ❑ Moderately sensitive to heat ❑ Very sensitive to heat

A1f) Do you have or have you recently had a fever?

❑ Yes ❑ No

A1f1). If yes, how often do you have fever?

❑ Constant ❑ Alternating chills and fever

A1f2). If yes, do you feel a

❑ Slight fever ❑ Moderate fever ❑ Strong fever

A1f3) Additional information: _____

_____

A2). SWEAT

A2a Excluding when you exercise, do you have a tendency to sweat?

❑ Yes ❑ No

A2a1).If yes, how much do you sweat?

❑ Slight sweating ❑ Moderate sweating ❑ Heavy sweating

A2b) Do you experience sweating that occurs at night?

❑ Yes ❑ No

A2b1). If yes, how much do you sweat?

❑ Slight sweating ❑ Moderate sweating ❑ Heavy sweating

A2b2) Additional information: _____

_____

A3). HEADACHE

A3a) Do you experience headaches?

❑ Yes ❑ No

If yes,

A3a1) Where do you experience your headaches?

❑Temporal L(left side) ❑Temporal R(right side) ❑Occipital(back of head)

❑ Frontal(forehead) ❑Vertex (top of head)

A3a2) What type of headache do you experience?

❑ Migraine

❑ Stress-related

❑ Cluster headaches (headaches that come as batches after a pain-free interval)

A3a3) Is your headache:

❑ Constant ❑ intermittent

A3a4) How often do you experience your headaches?

❑ Daily ❑Every 2-3 days ❑ Every 4-6 days ❑ Weekly ❑ Fortnightly

❑ Monthly ❑ 3 monthly ❑ 6 monthly

A3a5) Is the headache pain:

❑Stabbing/Throbbing ❑Distending ❑ A Pressure sensation

❑Moving ❑Dull

A3a6) How long have you been experiencing headaches?

❑ < 2 weeks ❑ 2-4 weeks ❑ 1-3 months ❑ 3-6 months ❑ > 6 months

A3a7) When do you experience your headaches?

❑ Morning ❑ Afternoon ❑ Evening ☐Anytime

A3a8) How long does the headache last?

❑ Short (< 30-60 min) ❑ Long (> 1 hour)

A3a9) What causes or increases your headaches? .....

.....

A3a10) What relieves your headaches? .....

.....

A3a11) Do you use medication for your headaches ?

❑yes ❑No

A3a12) If so, what medication do you use? .....

.....

A3a13) Are there any accompanying symptoms? .....

.....

A3a14) Additional information: _____

_____

A4). DIZZINESS AND VERTIGO

A4a) Do you experience dizziness?

❑Yes ❑ No

If yes,

A4a1) How long have you been experiencing dizziness?

❑ < 1-2 weeks ❑ 2-4 weeks ❑ 1-3 months ❑ 3-6 months ❑ > 6 months

A4a2) How often do experience dizziness?

❑ Daily ❑every2-3 day ❑every4-6 days ❑ Weekly ❑ Fortnightly

❑ Monthly ❑ 3 monthly ❑ 6 monthly

A4a3) How long does the dizzy attack last?

❑ Short (< 30 min) ❑ Long (> 30 min)

A4a4) When do you have the dizziness?

❑ Morning ❑ Afternoon ❑ Evening

A4a5) What causes or increases the dizziness? .....

A4a6) What relieves the dizziness? .....

A4a7) Do you use medication for dizziness?

❑yes ❑ No

A4a8) If so, what medication do you use

A4a9) Additional information: _____

_____

A5). BODY PARTS

A5a) Do experience numbness in any part of your body?

❑Yes ❑ No

If yes,

A5a1) Which parts feel numb?

RIGHT ❑ Fingers ❑ Hand ❑ Arm

❑ Toes ❑ Foot ❑ Leg

	☐ Face	☐ head	☐Neck	☐Upperback
	☐Midback	☐Lower back	☐Hip	
LEFT	❑ Fingers	❑ Hand	❑ Arm	
	❑ Toes	❑ Foot	❑ Leg	
	☐ Face	☐head	☐Neck	☐Upperback
	☐Midback	☐Lower back	☐Hip	

A5a2) Do you experience any general heavy sensation of body?

❑ Yes ❑ No

A5a3) Additional information:

A5b). Do you experience any pain in the body?

❑ Yes ❑ No

If yes,

A5b1) Which part is painful?

RIGHT	❑ Fingers	❑ Hand	❑ Elbow	❑ Arm
	❑ Toes	❑ Foot	❑ Knee	❑ Leg
	☐Face	☐Neck	☐Upperback	☐Midback
	☐Lower back	☐Hip		
LEFT	❑ Fingers	❑ Hand	❑ Elbow	❑ Arm
	❑ Toes	❑ Foot	❑ Knee	❑ Leg
	☐Face	☐Neck	☐Upperback	☐Midback
	☐Lower back	☐Hip		

A5b2) Additional information:

A6). URINE

A6a) What is the colour of your urine?

❑ Clear (Colourless) ❑ Light Yellow ❑ Dark Yellow

A6b) How much urine do you pass?:

❑ Little amount ❑ Moderate amount ❑ Large amount

A6c) Do you have to urinate often?

❑ Yes ❑ No

A6c1) If yes, how often do you go during the day?

☐1-4 times ☐5-7 times ☐8-10 times ☐>10 times

A6d) Do you have to urinate during the night?

❑ Yes ❑ No

A6d1) If yes, how often do you go?

☐1-2 times ☐3-4 times ☐5 times ☐>5times

A6e) How difficult is it to start the flow of urine?:

❑No difficulty ❑Some Difficulty ❑Moderate Difficulty ❑Severe difficulty

A6f) Is the flow of urine:

❑Even ❑Uneven (Stop/Start)

A6g) Do you have urine retention i.e. are you unable to completely empty the bladder?

❑ Yes ❑ No

A6h) Do you have any urine leakage?

❑ Yes ❑ No

A6i) Do you have pain or burning on urinating?

❑ Yes ❑ No

A6j) Do you experience bed-wetting?

❑ Yes ❑ No

A6k) Does your urine have a strong smell?

❑ Yes ❑ No

A6l) Additional information: _____

_____

A7). STOOLS

A7a). How often do you use your bowels each day?

❑ < 1/day ❑ 1-2/day ❑ > 2/day

A7b). How would you describe your stools?

❑ watery ❑ Loose ❑ Soft ❑Firm ❑ Hard ☐Alternating loose and hard

A7c). Do you have any leakage of stools?

❑ Yes ❑ No

A7d). Do you experience constipation?

❑ Yes ❑ No

A7e). Do your stools have a foul odour?

❑ Yes ❑ No

A7f). Do you have blood in your stools?

❑ Yes ❑ No

A7f1). If yes, what is the colour of the blood?

❑ Bright red ❑ Dark red ❑ Purple

A7g). Have you noticed any change in the colour of your stools?

☐Yes ☐No

A7g1). If so, what changes have you noticed and when did this occur?

_____

A7h) Additional information: _____

_____

A8). APPETITE

A8a) How is your appetite?

❑ Poor ❑ Good ❑ Excessively hungry

A8b) Do you eat at regular times each day or do you eat irregularly?

☐Regularly ☐Irregularly

A8c) Do you skip meals regularly?

❑ Yes ❑ No

A8d) How do you feel after you skip a meal?

❑ Tired ❑ Irritable ❑ Feel Cold ❑ No Effect

A8e) Do you experience any particular taste in the mouth?

❑ No particular taste ❑ Sweet taste ❑ Salty taste ❑ Bitter taste ❑ Sour taste

❑ Pungent taste ❑ Bland taste ❑ Greasy taste ❑ Inability To Taste

A8f) How do you feel after eating?

❑ Normal ❑ Nauseous ❑ Bloated ❑ have belching or burping ❑ Tired

A8g) Do you crave any particular foods?

❑No ❑Fried foods ❑Spicy foods ❑Sweet foods

❑ Salty foods ❑Bitter foods ❑Sour foods

A8h) Do you prefer cold or hot foods?

☐Cold foods ☐Hot foods

A8i) Do you prefer raw or cooked foods?

☐Raw foods ☐Cooked foods

A8j) Do you consume dairy foods?

☐Yes ☐No

A8k) Additional information: _____

_____

A9). THIRST & DRINK

A9a) Do you have thirst (desire to drink)?

❑ Yes ❑ No ❑ Yes, but no desire to drink

A9b) Do you have excessive thirst?

❑ Yes ❑ No

A9c). Do you have a preference for hot or cold drinks?

❑ Cold ❑ Moderate temperature ❑ Hot

A9d) Additional information: _____

_____

A10). CHEST

A10a). Do you experience any abnormal sensation in the chest?

❑ Yes ❑ No

A10a1) If yes, the sensation is:

❑Pain ❑Oppressed feeling ❑Fullness/Distending ❑Other sensation

A10b). Do you cough up or spit out phlegm on a daily basis?

❑ Yes ❑No

A10c) Additional information: _____

_____

A11). ABDOMEN

A11a) Do you experience pain in the abdomen (stomach)?:

❑ Yes ❑ No

If yes,

A11a1) Where do you feel the pain?

❑ Epigastric(upper abdomen)

❑ Umbilical(centre abdomen)

❑ Below Umbilicus(lower abdomen)

❑ Left Hypochondriac(left side of abdomen)

❑ Right Hypochondriac(right side of abdomen)

❑ Wandering or moving pain

A11a2) Would you describe the sensation as:

❑ Stabbing ❑ Distending (fullness) ❑ Colicky (spasms) ❑ Other

A11a3) Relieved by heat?

❑ Yes ❑ No ☐ Don't know

A11a4) Aggravated by heat?

❑ Yes ❑ No ☐ Don't know

A11a5) Relieved by pressure?

❑ Yes ❑ No ☐Don't know

A11a6) Aggravated by pressure?

❑ Yes ❑ No ☐Don't know

A11b) Do you have stomach bloating?

❑ Yes ❑ No

A11b1) If yes, when? .....

A11b2)Additional information: _____

_____

A12). EARS AND EYES

A12a) How is your hearing?

❑ Normal ❑ Slight Decrease ❑ Significant Decrease

A12b) Do you have tinnitus?

❑ Yes ❑ No

A12b1) If yes, is it?

❑ Slight tinnitus ❑ Moderate tinnitus ❑ Severe tinnitus

A12c) Do you have blurred vision that is not associated with short or long sightedness?

❑ Yes ❑ No

A12d) Do experience dry eyes?

❑ Yes ❑ No

A12d1) If yes, are they?

❑ Slightly dry ❑ Moderately dry ❑ Severely dry

A12e) Do you have watery eyes?

❑ Yes ❑ No

A12e1) If yes, are they?

❑ Slightly watery ❑ Moderately watery ❑ Severely watery

A12f) Are you sensitive to light?

❑ Yes ❑ No

A12g) Are you sensitive to wind?

❑ Yes ❑ No

A12h) Additional information: _____

_____

A13). SLEEP

A13a) How is your sleep?:

❑ Poor (that is, light or broken, and you wake feeling unrefreshed)

❑ Good (that is, you wake feeling moderately refreshed)

❑ Very good (that is, you wake feeling very refreshed)

A13b) How much sleep to you usually have per night?

❑ < 7 hours ❑ 7-9 hours ❑ > 9 hours

A13c) Do you dream in your sleep?

❑ Never ❑ Seldom ❑ Occasionally ❑ Frequently

A13d) Do you have difficulty falling asleep initially?

❑ Yes ❑ No

A13e) Do you wake up during the night?

❑ Yes ❑ No

A13e1) If yes, how often do you wake?

❑ once ❑ twice ❑ > 2 times

A13e2)Additional information: _____

_____

A14). ENERGY LEVELS OVER THE PAST 2 WEEKS

A14a) How has your energy been over the last 2 weeks?

❑ Little energy ❑ Moderate amount of energy ❑ Abundant energy

A15). SHORTNESS OF BREATH

A15a) Do you experience (unexplained) shortness of breath?

❑ Yes ❑ No

A16). EMOTIONS OVER PAST WEEK

A16a) What emotions have you felt over the past week?

❑ Calmness ❑ Anger/irritability ❑ Grief/sadness

❑ Anxiety/worry ❑ Fearfulness ❑ Excessive happiness

❑ Excessive thinking

A16b) Additional information: _____

_____

A17). FOR WOMEN:

A17a) Have you reached menopause?

❑ Yes ❑ No

If no,

A17a1) Where are you in your menstrual cycle?

❑N/A ❑1st week ❑2nd week ❑3rd week ❑4th week

A17a2) Do you have a regular menstrual cycle (27-29 days)?

❑ Yes ❑ No

A17a3). How long does the bleeding last?

❑ 3 or less days ❑ 4 - 7 days ❑ 8 days or more

A17a4) What is the volume of blood on the day that you bleed the heaviest?

❑ Less than 4 pads/tampon changes per day ❑ 4 changes/day ❑ More than 4 changes

A17a5) Is there clots in the menstrual blood?

❑ Yes ❑ No

A17a6) What is the colour of your menstrual blood?

❑ Pale Red ❑ Normal Bright Red ❑ Dark Red ❑ Purple

A17a7) Do you suffer from menstrual or period pain?

❑ Yes ❑ No

A17b) Do you experience vaginal discharge?

❑ Yes ❑ No

A17c) Additional information: _____

_____

A18). KNEE JOINT

A18a) Do you have knee pain?

❑ Yes ❑ No

If yes,

A18a1) Which knee is painful?

☐Right knee ☐Left knee ☐Both knees

A18a2) Where is your knee pain?

❑Inside of the knee(medial) ❑Outside of the knee (lateral) ❑Both sides of the knee

A18a3) Would you describe your pain as:

❑Stabbing/Throbbing ❑Heavy ❑Dull ❑Burning ❑Grinding

A18a4) Is your knee pain:

❑ Constant ❑ Variable (only sometimes present) ❑Moving

A18a5) How long have you had your knee pain?

❑ < 1 month ❑ 2-6 months ❑ 7-12 months ❑ 2-5 years ❑ > 6 years

A18a6) How long does the pain attack last?

❑ Short duration (< 30-60 min) ❑ Long duration (> 1 hours)

A18a7) Does the type of weather increase your knee pain?

☐No ☐cold weather ☐damp weather ☐hot weather ☐windy weather

A18a8) What causes or increases your knee pain? .....

.....

A18a9) What relieves your knee pain? .....

.....

A18a10) Additional information: _____

_____

A18b) Do you have stiffness in the knees?

❑ Yes ❑ No

If, yes

A18b1) When is the knee stiff?

❑Morning ❑Afternoon ❑Evening ❑Only occasionally

A18b2) How long does the stiffness last?:

❑ < 30 minutes ❑ 30 minutes – several hours ❑ All the time

A18b3) What causes or increases the stiffness? .....

.....

A18b4) What relieves the stiffness? .....

A18b5) Additional information: _____

_____

A18c) Do you have swelling of the knee joint?

❑ Yes ❑ No

If, yes

A18c1) Which knee is swollen?

☐Left knee ☐Right knee ☐Both knees

A18c2) Where is the swelling?

❑Inside knee (medial) ❑Outside knee (lateral) ❑Whole knee

A18c3) How does the swelling feel?

❑No sensation ❑Hot sensation ❑Cold sensation ❑Other sensation

A18c4) How long have you had knee swelling?

❑ < 2 weeks ❑ 3-4 weeks ❑ 2-6 months ❑ > 6 months

A18c5) What causes or increases the knee swelling? .....

.....

A18c6) What relieves the knee swelling? .....

A18c7) Additional information: _____

_____

A18d) How is your knee strength?

❑ Normal

❑ Weaker than before, but does not affect physical activity

❑ Weaker than beforeand affects physical activity

❑ Cannot walkand need assistance

A18d1) How long have you had knee weakness?

❑ No ❑ < 1 month ❑ 2-6 months ❑ 6-12 months ❑ > 1 year

A18d2) Is there any muscle loss?(atrophy)

❑ No ❑ A little, but not obvious ❑ Notable muscle loss (atrophy)

A18d3) Additional information: _____

_____

A19) OTHER COMPLAINTS:

_____

_____

B. INSPECTION (VISUAL)

B1). WITH SPIRIT

B1a) Strength of spirit: ❑ Poor ❑ Moderate ❑ Strong

B1b) Additional information: _____

_____

B2). COMPLEXION

B2a) Colour of complexion:

❑Normal ❑Yellow ❑Pale ❑Red ❑Green ❑Black

B2b) Skin lustre: ❑ Dry skin ❑ Moist skin (lustrous)

B2c) Additional information: _____

_____

B3). HAIR ON HEAD

B3a) Amount: ❑ Plentiful ❑ Thinning ❑ Receding forehead ❑ Balding

B3b) Appearance:❑ Dry ❑ Lustrous

B3c) Additional information: _____

_____

B4). PHYSICAL BUILD

B4a) Body frame: ❑ Small ❑ Medium ❑ Large

B4b) Musculature: ❑ Solid/Muscular ❑ Thin/Flaccid Muscles

B4c) Body fat: ❑ Underweight ❑ Moderate Weight ❑ Overweight

B4d) Additional information: _____

_____

B5). POSTURE AND BODY MOVEMENT

B5a) Sitting posture: ❑ Upright ❑ Slumped

B5b) Body movement walking: ❑ Restricted: ❑ Unrestricted

B5c) Additional information: _____

B6). TONGUE BODY

B6a) Size: ❑ Small ❑ Moderate ❑ Enlarged (Swollen) ❑ Thin

B6b) Teeth marks: ❑ Yes ❑ No

B6c) Colour: ❑ Pale ❑ Pink (Normal) ❑ Red Crimson

❑ Purple ❑ Red Tip

B6d) Constitution of tongue: ❑ Soft ❑ Firm

B6e) Cracks or fissures: ❑ Yes ❑ No

B6f) Spots (raised papillae): ❑ Yes ❑ No

B6g) Trembling: ❑ Yes ❑ No

B6h) Deviation of tongue: ❑ Yes ❑ No

B6i) Additional information: _____

_____

B7). TONGUE COATING

B7a) Presence of coating: ❑ Yes ❑ No

B7b) Thickness of coating:

❑ Absent ❑ Very Thin (Nearly Absent) ❑ Thin (Normal) ❑ Thick

B7c) Quality of coating:

❑ Dry ❑ Moist (normal) ❑ Sticky/greasy ❑ Curdy ❑ Peeled

B7d) Colour of coating:

❑ White ❑ Yellow ❑ Grey ❑ Green ❑ Black

B7e) Additional information: _____

_____

B8). SENSE ORGANS

B8a) Colour of Lips: ❑ Pale ❑ Pink/Red ❑ Bright Red ❑ Purple

B8b) Additional information: _____

_____

C. AUSCULTATION AND OLFACTION

C1). STRENGTH OF VOICE

❑ Soft ❑ Moderate ❑ Loud

C2). BREATHING SOUNDS

❑ Normal (silent) ❑ Wheezing ❑ Heavy/laboured

C3) Additional information: _____

_____

D. PALPATION

D1). LEFT PULSE

D1a) Speed:

❑ Slow (below 60 beats/min) ❑ Moderate (60-90 beats/min) ❑ Fast (over 90 beats/min)

D1b) Location: ❑ Superficial ❑ Mid-Level ❑ Deep

D1c) Force: ❑ Weak ❑ Moderate ❑ Forceful

D1d) Additional information: _____

_____

D2). RIGHT PULSE

D2a) Speed:

❑ Slow (below 60 beats/min) ❑ Moderate (60-90 beats/min) ❑ Fast (over 90 beats/min)

D2b) Location: ❑ Superficial ❑ Mid-Level ❑ Deep

D2c) Force: ❑ Weak ❑ Moderate ❑ Forceful

D2d) Additional information: _____

_____

D3). PALPATION OF HANDS

D3a) Temperature of hands: ❑ Cold ❑ Warm ❑ Hot

D3b) Moisture of skin of hands: ❑ Sweaty ❑ Neither sweaty nor dry ❑ Dry

D3c) Additional information: _____

_____

E. DIAGNOSIS SUMMARY

E1. Analysis of Signs and Symptoms

E1a. Internal or external syndrome:

❑ Interior ❑ Exterior ❑ Semi Interior/Semi Exterior

E1b. Heat or cold syndrome:

Heat: ❑ (slight) ❑ (moderate) ❑ (strong)

Cold: ❑ (slight) ❑ (moderate) ❑ (strong)

E1c. Excess or deficiency:

Excess: ❑ slight ❑ moderate ❑ strong

Deficiency: ❑ slight ❑ (moderate ❑ strong

E1d. Yin or Yang:

Yin ❑ ❑ Yang

E1e. Which Zang organs are involved?

E1f. Which Fu organs are involved?

E1g. Which meridians are involved?

E2. Which were the principal diagnostic criteria (signs or symptoms) that lead to your diagnosis?

.....

.....

E3. Rank the diagnostic criteria that lead to your diagnosis in order of importance (1=most important)

E3a ..... (Most important sign/symptom)

E3b .....

E3c .....

E3d .....

E4. Overall syndrome diagnosis: .....

.....

E5. Predominant syndrome (if more than one syndrome): .....

.....