

**GP-TCM Guidelines for randomized controlled trials
investigating Chinese herbal medicine (CHM)**

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1. Introduction

The aim of this document is to develop guidelines that can be applied to improve the design and rigour of Randomized Controlled Trials (RCT's) investigating the use of Chinese herbal medicine (CHM). It is not intended as a comprehensive research strategy for CHM although there are issues relating to the use of RCT's that will be relevant when using other research methods such as observational studies, case controlled studies, surveys and qualitative research.

2. Objectives

The primary objectives of this paper are:

- to introduce CHM as a complex medical intervention
- to explore the range and possibilities of research options using the RCT model
- to propose ways in which this traditional medical system and these modern experimental tools can interact successfully to create sound evidence based practice.

The initial sections of these guidelines describe the real and already evident risk that subjecting CHM to the scrutiny of RCT's can distort the practice of CHM in such a way as to undermine the relevance of the data that is produced. However, it is our contention, that if the RCT design is thoughtfully used and sensitive to the nuances of CHM, especially individualized prescriptions, then it can be a rigorous and pragmatic way of investigating the contribution that CHM can make to contemporary health care.

3. Introduction to CHM

3.1 Current status

Chinese herbal medicine (CHM) is a key component of the system of Chinese Medicine (CM) that has been practiced, developed and recorded for more than two thousand years

within China and other East Asian countries. The process of transmission of CM to the West started gradually around 400 years ago (Unschuld 1998) but in recent years it has gathered momentum and CM is now providing a rapidly increasing contribution to health care in all the major industrialised countries.

In China today CHM is taught as an undergraduate course at 47 universities and colleges and is investigated at 139 institutes for Traditional Chinese Medicine (TCM) research. In 2008 there were 218,044 registered TCM doctors practising in the 3,063 hospitals in China offering TCM treatments. The gross value of CHM products in China in 2008 was estimated to be 216.65 billions RMB (\$31 billion) accounting for over a quarter of the total expenditure on all medicines (SATCM 2008, MOH 2008).

The global herbal medicine market for all herbal traditions is growing at an average of 13% per annum and was estimated to have reached \$40 billion in 2006 (Kaphle et al 2006).

The extent of the CHM market within the EU has not been properly assessed. In Germany over 500 tonnes of traditional CHM were imported in 2005 (Dobos et al 2005) and there is a specialist CM hospital (Melchart et al 2003) and smaller state supported institutes prescribing CHM therapies.

Data is similarly sparse from other EU countries. In the UK for example there are no precise figures on the number of CHM practitioners or the extent of the CHM market. The two main CHM registers in the UK contain over 1100 members but this does not include unregistered practitioners working in high street retail outlets. According to a recent survey of 2,032 UK adults (MORI 2008), conducted for the Medicines and Healthcare products Regulatory Agency, 5% of the adult population (approximately 2.5 million) has already used CHM. This is a significant section of the population.

These figures, imprecise as they are, point to the substantial role of CHM within China and the developing role of CHM in contemporary health care globally and in the EU.

3.2 The practice of Chinese herbal medicine (CHM)

CHM has its own unique understanding of the aetiology, patho-physiology, diagnosis and treatment of disease that has developed over two thousand years of experimentation and recorded observation. This corpus of knowledge includes the accumulated insights of experienced individual practitioners and in recent years has been bolstered by data derived from observational studies, RCT's and systematic reviews.

Unsurprisingly CM has developed over hundreds of years into a medical system that contains diverse and sometimes contradictory accounts of disease. It has been convincingly described as a form of medical pluralism (Scheid 2002). Unlike Western medicine where technological progress encourages rapid, comprehensive and continuous revision, CM essentially uses the same methods of diagnosis and treatment that were prevalent in the pre-industrial era. For those not familiar with the practice and terminology of CHM it may appear a rather confusing and arcane system of medicine. In Western medicine Galenic or Hippocratic texts are anachronisms of historical interest only. In CM the equivalent texts provide the basic building blocks of the medical system and still inform much contemporary clinical practice. As a result historical records of hundreds of years of empirical experience are profoundly relevant to contemporary CM practice. However, there is very little research comparing the diverse strands to emerge from this long history and there is no single tradition that can be considered to provide an uncontested basis for best practice.

Recent attempts within the Peoples Republic of China to synthesize a standardised and modernised version of these traditions have led to the development of Traditional Chinese Medicine (TCM). This is the contemporary version of CM that is practiced and researched throughout hospitals in modern day China. Whilst elements of this 20th century development have proved successful this process has also come at a price and has been associated with a reduction in the diversity, complexity and subtlety of CM (Unschuld 1998, Scheid 2002 & 2007).

CHM typically involves the use of herbal formulae comprising of a number of separate herbal ingredients selected from a *Materia Medica* of several thousand herbs. The formulae are prescribed according to established TCM principles of diagnosis. Historically these herbs have been prepared in a number of ways including boiled decoctions, dried herbal powders, pills, and less commonly as medicinal wines or tinctures. In China today, some of the ancient classical formulae have been developed into Chinese proprietary medicines after passing through a strict clinical examination under the new drug approval procedures. These medicines are regulated by the Chinese State Food and Drug Administration and are widely used in Chinese hospitals as capsules, granules or tablets, and may also be delivered as an intravenous infusion.

Best practice of CHM is usually considered to require the use of individualised herbal formulations that are adapted to address the particular needs and the changing clinical presentations of each patient (Bensky et al 1986, Farquhar 1994). This makes CHM a dynamic and highly responsive system of medicine that resonates strongly with the increasing emphasis within Western medicine for the use of both combination therapies to achieve optimum benefits and individualised treatments to take into account genetically variable responses to modern drugs.

CHM has also been responsible for a number of adverse reactions. Adulteration with steroids in skin creams (Keane 1992), the use of nephrotoxic *Aristolochia* species in Belgium and other EU countries (Nortier et al 2000, Debelle et al. 2008), and rare instances of idiosyncratic liver toxicity (Perharic et al 1995), have made quality control and statutory professional regulation important public health issues and have left many conventional physicians understandably suspicious of the safety of CHM.

There is then a clear need to investigate both the effectiveness and the potential adverse effects of CHM so that it can be assessed in a rational and consistent manner, free from the positive bias of its exponents and the prejudice of those who believe it is dangerous quackery (Colquhoun 2009).

3.3 CHM research

It has been estimated that there are over 17,000 CHM clinical trials that have been reported in East Asian medical journals (Tang et al 1999, Wang et al 2007) although the reliability of many of these studies has become questionable owing to a lack of methodological rigour (Wu et al 2009) and apparent publication bias (Tang et al 1999). In the West recent peer reviewed research has demonstrated the effectiveness of an individual herb Lei Gong Teng (*Radix Tripterygii Wilfordii*) in the treatment of rheumatoid arthritis (Goldbach-Mansky et al 2009) and herbal combinations in the treatment of irritable bowel syndrome (Bensoussan et al 1998), atopic eczema (Sheehan et al 1992), and as an adjunctive treatment in leukaemia (Wang et al 2008).

At the beginning of 2009 there were 42 Cochrane Reviews on CHM (Manheimer 2009) and since then additional reviews have been added. Manheimer's review concluded that 19 of these Cochrane reviews provided preliminary evidence of the possible benefits of CHM in the treatment of a number of conditions. However the poor methodological quality of CHM clinical trials leads to the majority of trials being excluded from a Cochrane review and it is an almost standard refrain at the end of each review that more rigorous research is required to substantiate these preliminary findings-although this is also true for most reviews of conventional medicine.

CHM uses herbal products that contain highly active compounds that have been extensively researched and in some instances developed into pharmaceutical drugs. These include single constituents such as Ephedrine from Ma Huang (*Radix Ephedra sinensis*), Artemisinin from Qing Hao (*Herba Artemisiae annuae*) and Genistein from (*Glycine max*) which are just a few examples of how some of these active compounds have been refined into conventional medicines. In addition, in China the national essential drug list published in August 2009 contained 102 Chinese herbal medicines that were all reimbursed by public health care insurance (<http://www.sda.gov.cn/WS01/CL0053/40800.html>).

3.4 Methods of administering CHM

Until relatively recently the prolonged boiling of dried herbs in water to make herbal ‘soups’ or decoctions was by far the commonest method of administering CHM (Bensky 1986). In the past few decades it has become possible and increasingly popular to use concentrated powdered herbal extracts produced by spray drying decoctions of individual herbs or herbal formulae comprising several different ingredients. These powders can then be encapsulated, pressed into tablets, or reconstituted by the addition of hot water. They have the advantage of being easy to use and have gained considerable popularity as a convenient way to access CHM.

However these advantages may come at a price. Chromatographic evidence indicates that decoctions provide a different composition and a different concentration of available compounds than powdered extracts (Leung, Fong & Xue 2006, Chen LH et al., 2006; Ma YP et al., 2006). These compounds may be important factors in the therapeutic actions of a herb or formula and may underpin the detailed records of clinical actions that have been recorded over the past 2000 years and which still provide the basis for much contemporary clinical practice.

One major difference between the administration of powders and decoctions is that in many instances powdered formulae may simply involve individual herbal powders being combined together without undergoing a prolonged cooking process. This may lead to a loss of potential interactions between herbal compounds that occur as herbs are simmered together in water and again may alter the therapeutic effects of a herbal formula. There is also anecdotal evidence suggesting that powders derived by spray drying decoctions may not be as efficacious as identical recipes prepared as decoctions. However a recent systematic review of 56 comparative trials of powders versus decoctions conducted in China found no significant differences in the effectiveness between these two methods of herbal preparation (Luo et al awaiting publication). Unfortunately these findings were compromised by the poor quality of the trials included in the review, and considerable more research is required before there can be any definitive clarity about the comparative effectiveness of herbal decoctions and powders.

Decoctions also have their own set of limitations. Pharmacologists are critical of this approach because of their unstable composition. Identification and standardization of the bioactive compounds within a decoction is a tremendous challenge that is regarded to be almost impossible. The availability of active compounds varies according to the quality and quantity of the raw material and the cooking times used for preparation. In addition heat sensitive ingredients are destroyed and aromatics, the often-designated active principles, evaporate during the cooking process. As a consequence researchers and practitioners frequently reject decoctions in favour of pharmaceutical products such as tablets or powders, which can be standardized and subject to more rigorous quality control.

Unfortunately in most cases the active ingredients within decoctions are not known. This makes it difficult to standardize the herbal product and impossible to guarantee that important compounds that may be available in decoctions are captured within the extraction process used to prepare powdered extracts. “Modern” extraction methods for the preparation of Chinese herbal medicines, therefore, are limited by this requirement to identify single bioactive compound(s). In practice much of the therapeutic activity of herbs is almost certainly the result of multiple compounds.

An example of these limitations is evident from the mass bio-prospecting effort of the National Cancer Institute of the US which screened about 114,000 extracts from an estimated 35,000 plants to yield only three clinically significant cancer chemotherapeutics (Cragg and Boyd 1996). Thus, the yield of huge screening projects for the identification of single bioactive compounds appears to be poor. If provision was made to investigate the synergistic effects of multiple compounds then this might elevate the yield (Ulrich-Merzenich et al. 2007). In practice, without proper knowledge of the bioactive compounds, pharmacological methods of extraction may result in a reduction or loss of therapeutic effect and a change in the safe parameters for a herb. This may be to such an extent that these approaches can no longer be considered part of traditional CHM.

What then are the implications for research into CHM? Despite their limitations, decoctions facilitate complex chemical reactions between herbs that provide a basis for the therapeutic effects that have been observed and developed over previous centuries. Moving away from

this approach, either by simply aggregating individual herb powders or extracting and standardizing active compounds, risks changing the therapeutic actions of CHM and may result in unknown and potentially unsafe side effects. It makes sense, if we are to locate research within the broad range of Chinese medical practices, to respect traditional methods of preparation. Consequently we recommend the following staged process for CHM research:

1. Initially researchers into CHM should endeavour to use herbal decoctions as the starting point for research into good practice of CHM. An analysis of pharmacological relevant ingredients where possible should be provided to help safeguard the comparability of different studies . Plant monographs (Wagner, Bauer, Melchart 2011) can be used as source to decide what should be measured.
2. If the practical difficulties of using liquid decoctions are insurmountable (see below) then concentrated, powders can provide a pragmatic alternative. Ideally, rather than simply combining individual powders, we recommend that powdered extracts are derived, at least in part, from a formula of several herbs being decocted together before being spray dried and turned into powdered extracts. This approach is more likely to preserve the composition of ingredients formed during the cooking process and provides a starting point for the research process.
3. Subsequent research using different methods of extraction and delivery could then use these data as a of baseline measurement for good practice which should be matched or superseded by the new form of intervention.

3.5 Addressing the practical difficulties of using herbal decoctions

There are obvious practical difficulties involved in researching CHM decoctions. Traditional methods of boiling are time consuming to prepare and result in a strong tasting liquid that can be difficult to drink. Compliance can be compromised by these factors. In addition the distinctive taste of herbal decoctions means that it may be problematic preparing a convincing, inert placebo decoction to be used within a control group. It is for these reasons

that most experimental clinical research into CHM uses either herbal tablets or encapsulated herbal powders that are easier to take and more readily mimicked by inert controls (placebos).

Recently however, using imported technology from Korea and China, it has become possible to pre-cook herbal decoctions and dispense them in sealed, separately packaged, daily dosages. This obviates the need for any preparation by the patient and leads to both an increased compliance and a more consistent end product. Not only does this facilitate the use of decoctions in clinical research but it also provides a route by which a convincing placebo control could be developed that mimicked the appearance of the active medicine. A feasibility study exploring the role of CHM in the treatment of endometriosis used a collection of vegetables and culinary herbs to replicate the strong taste and colour of a herbal decoction. The placebo decoction was shown to be plausible and it enabled rigorous double blinding to take place in a trial using individualised active decoctions (Flower et al 2011). Concerns about the therapeutic inertia of the ingredients that constituted the placebo would be addressed if food colourings and flavourings were used instead of dried plant material and this will constitute the next stage in the development of this new methodology for testing CHM.

3.6 Discussion

This section of these guidelines is both complex and controversial. There is a real need for rigorous research to investigate the importance of the relationship between how herbs are prepared and their therapeutic activity. Traditional use suggests that herbal decoctions should be considered as the basic ‘unit’ of CHM and there is some, limited evidence to support this view. Ideally, in order to reproduce traditional practice, these decoctions should be taken in liquid form and it has been demonstrated that it is possible to conduct a double blind RCT using this approach.

Where liquid decoctions are not possible powdered extracts can be prepared from decoctions using several ingredients which can then be re-constituted, administered as granules, pills, tablets or capsules, or in some instances as a herbal injection. Each of these various herbal

products has advantages and disadvantages (see Table 1) and researchers should be mindful that these may influence their therapeutic effects.

Some of the considerations that may influence which method of administering herbs is selected include:

- The form of herbal delivery in usual practice
- Compliance
- Cost
- Ability to provide a placebo control
- Requirements for GMP and ability to meet national quality control standards
- Whether individualized treatments are being tested
- The need for blinding

It is important that research into CHM engages with these dilemmas and finds rigorous and creative ways to help resolve them. The ‘mode’ of administration may convey the ‘message’ of the herbal treatment, and it is important to acknowledge this when reporting results and when seeking to generalise these results into the day-to-day practice of CHM.

Table 1: Advantages and disadvantages of the main different methods of preparing CHM

Method of preparation	Advantages	Disadvantages
Decoctions	<ul style="list-style-type: none"> • Large range of primarily water soluble herbal compounds, • Traditionally used • Individualised treatment • Easily adapted • Can be given in large dosages • Easier to use DNA testing to ensure species authentication. 	<ul style="list-style-type: none"> • Expensive and complex to deliver? in the West • Time consuming to prepare • Strong taste and smell • Difficult to match in placebo controlled trials • Difficult to standardize • Potential loss of volatile ingredients • Change of ingredients due to the influence of oxygen; this process is faster as decoctions have a higher reduction ratio (Hänsel, Spieß 2007)
Concentrated herbal powders or granules	<ul style="list-style-type: none"> • Consistent quality control • Subject to GMP • Easy to encapsulate • Can be individualized and adapted • Cheaper in the West. More expensive in China. • Easy to prepare a matched placebo 	<ul style="list-style-type: none"> • Potential loss of vital herbal compounds during the extraction process • Different compositions than decoctions and thus potentially different mode of action than decoctions • Anecdotally difficult to administer in large dosages without digestive problems
Tablets/Pills (traditionally prepared from water extractions or pressed powdered extracts)	<ul style="list-style-type: none"> • Cheapest • Subject to GMP • Easy to compare with placebo • Easy to take 	<ul style="list-style-type: none"> • Standardized • Potential loss of vital herbal compounds during the extraction process • Difficult to administer in large dosages
Injections	<ul style="list-style-type: none"> • Bypass digestive system • Strong action • Subject to GMP 	<ul style="list-style-type: none"> • Standardized • No traditional data relating to this method • No action via digestive system eg gut flora • Difficult to administer by herbalist • Safety concerns. Reports of adverse reactions have led to re-evaluation of the safety of herbal injections (http://www.sda.gov.cn/WS01/CL0055/39880.html)

In addition there are other formulations such as alcohol and water extracts taken internally and herbal plasters or essential oils that are suitable for topical use.

4. Researching CHM-special considerations.

In addition to the method of preparing CHM there are a number of other important considerations that need to be taken into account in CHM research. Despite the large number of clinical trials investigating CHM this work has been severely compromised by poor methodology leading to a lack of both rigour and relevance. It is clear that there are special challenges that arise when researching CHM. It is important that these are thoughtfully addressed during the development of a research protocol and that the RCT model which works well for pharmaceutical drugs is not simply transposed into a CHM context.

Instead we recommend that CHM researchers take a step backwards to reflect on these issues and to develop appropriate methodologies to capture the key elements of CHM practice. In accordance with the UK's Medical Research Councils guidelines (Craig et al 2008) on evaluating complex interventions it is advisable that CHM research adopts a phased approach to research involving:

- a development phase: this involves the initial conception of the research idea. Research ideas should emerge from positive experience in clinical practice and ideally address “effectiveness gaps”, resulting from either the sub-optimal management conditions by conventional medicine or where the use of a conventional medications that are expensive and/or likely to result in drug reactions and side effects for the patient. Once the basic concept for research has been selected it is then necessary to identify the evidence base and explore the underlying theory and practice of the intervention to ensure that the model used has validity.
- A feasibility/ piloting phase: to test procedures (for example the plausibility of a herbal placebo), to establish sources of recruitment, drop out rates, and to provide preliminary data that can be used to determine sample size

- An evaluation phase: involving clinical research including RCT's that are adequately powered to detect a treatment response and to assess the effectiveness of a CHM intervention.
- An implementation phase: to consider the longer-term effects of CHM treatment and to assess the take up of CHM and how it may be integrated into mainstream healthcare.

In practice these phases do not follow a simple linear development. For example a new model of best practice (Development phase) may be required after analysis of the results of a feasibility study, or a new pilot study may be necessary to clarify issues arising from a large clinical trial (Evaluation phase). Researchers must be sensitive to these kinds of issues when moving through developmental phases and be prepared to be flexible and responsive to new data as they emerge from the research process.

The important and defining features of CHM that should to be taken into account when designing CHM research protocols are considered below.

4.1 Whole systems research

CHM is often used as one component in a complex intervention that draws its therapeutic potential from more than just the specific effects of herbal medicines. This frequently involves providing dietary advice, discussing lifestyle choices, and perhaps also using treatments such as acupuncture as component parts of a whole system of healthcare. Using CHM within a complex intervention encourages the cultivation of the therapeutic relationship between practitioner and patient and provides a philosophical and linguistic framing that allows a patient to understand and contextualise their illness. These contextual factors have been shown to provide important therapeutic benefits (Patterson and Dieppe 2005). These are essential components of Traditional Chinese Medicine (TCM) and, if the research question relates to the effectiveness of CHM intervention, then they should not be excluded as unwanted confounders by over fastidious research design.

4.2 Identifying research stakeholders

The research question and the design for a research protocol should also take into account the interest of stakeholders, who are the end users of this information. Practitioners may gain some benefit from RCT's comparing rival CHM treatment regimes to answer questions relating to traditional diagnoses, herb and formulae selection, mode of administration, and dosage. Patients may be best served by pragmatic designs comparing the 'whole system' of CHM care to other treatment options with no attempt to separate the specific and contextual effects of treatment. Funding bodies may also prefer comparative designs but have an additional interest in economic evaluations of CHM treatment. For both patients and funders pragmatic designs that include more heterogeneous patients, a less standardised treatment protocol and patient centred outcomes are useful to inform decision-making. Researchers working to develop pharmaceutical style drugs from CHM will tend to focus on pre-formulated products with few ingredients that can be reliably standardized and delivered outside of the context of a traditional CHM consultation by Western medical practitioners or as an over the counter product.

4.3 Refining the research question

Defining the research question is the fundamental starting point from which the rest of the research design will follow. Different questions require different research models to provide the answers. For example:

- Questions relating to the specific efficacy of CHM in treating a particular condition will require an explanatory RCT (see section 5.3.1)
- Questions relating to the effectiveness of CHM intervention in normal practice will require a pragmatic design (section 5.3.2)
- Other questions may not require a RCT to provide the necessary data and can be better explored using other research methods (see Table 2)

Table 2. Matching a research question with an appropriate methodology.

Research question	Methodology
What is the efficacy of CHM for a specific disease or condition?	Placebo-controlled, double-blind, randomised clinical trial
What is the effectiveness of CHM in real world practice?	Pragmatic randomised trials
Are there side effects from CHM?	Observational study-longitudinal survey Case controlled study
What is the patient's experience of taking CHM?	Qualitative research
Which conditions seem to respond well to CHM?	Patient registries Observational study Cross sectional survey of practitioners
What are the active ingredients of a particular herb?	Laboratory experimentation
What is the economic cost of CHM for treating a disease?	Health economic evaluation

Once the primary orientation of the research question has been decided and an appropriate methodology selected then the question needs to be further refined.

The first prerequisite for refining a research question is to carry out a thorough literature search (Section 5.1). A literature search is an iterative and developmental process that will contribute directly and indirectly to protocol development. It will help to identify whether the research question has already been asked and also point out the strengths and weakness of previous research in addressing and answering this question.

A research question is likely to be answerable if it is explicit, focused and feasible. In other words, it should be possible to link the effect of an intervention explicitly to a specific outcome on a particular target population. There should be a very clear, simple primary question and a research method that will provide an answer – the trick is not to ask too many primary questions simultaneously even in a complex study. If there are multiple questions, then the primary research question must be given priority. The primary research question

must be framed so that it is both possible and practical to answer the question. The findings must be achievable within a reasonable period of time and within the bounds of the scientific and financial resources available. Factors that may allow for the misinterpretation of the study's findings, such as 'bias' and 'confounding', must be considered at the an early stage and the research questions then modified, so that an appropriate trial design eventually emerges. These are considered further below (section 5.4).

4.4 Defining 'good practice'

It is important to ensure that what is being researched is representative of good practice of CHM. Researching what is not practiced or what is not considered to be effective should be avoided. It should be noted that in a system of medicine that is highly pluralistic and lacking in extensive and rigorous comparative research, good practice will not be limited to a single CHM approach. In the context of these guidelines 'good practice' is defined as an approach consistent with the logic of CHM, with a clear and demonstrable professional consensus, and preliminary evidence of effectiveness.

A literature review (see section 5.1) will provide data that can be used in the process of defining good practice of CHM. Other ways of establishing good practice guidelines include developing professional consensus by using methods such as the Delphi process (Flower et al 2007), expert consensus meetings or action research. Ideally defining good practice should emerge from a synthesis of these approaches.

It is recommended that if a research team has no experience of the clinical practice of CHM then attempts should be made to collaborate with experienced practitioners to ensure that model validity, including good practice, is achieved.

4.5 Pattern diagnosis within CHM

CHM employs a number of distinctive systems of diagnosis. In modern China and in many Western countries the dominant model is Traditional Chinese Medicine (TCM). TCM groups

apparently disparate symptoms together with representative signs of tongue and pulse analysis into commonly occurring syndromes or patterns of disease (Bian Zheng). Patterns describe the origins of a disease, how it manifests, and ways it can be treated. For example a woman presenting with digestive problems, fatigue, dizziness, premenstrual syndrome and temporal headaches with a pale tongue and a thready and wiry pulse may be diagnosed with Spleen Qi deficiency, Blood deficiency and Liver Qi stagnation. A treatment would be designed to address these patterns, a classical formula would typically be selected as a model and then adapted to the particular presentation of this patient (see Table 3).

Recently metabonomic analysis has provided some objective verification of the existence and value of these patterns (Van Wietmarschen et al 2009, Yan B et al 2009). This is an exciting application of modern systems biology to CHM and it could provide biologically plausible pathways to explain the mechanisms underlying CHM intervention.

Pattern differentiation is an integral part of CHM and should have an important role in CHM research. Clinical trials have started to use this approach to inform sub-group analyses to provide preliminary evidence of, for example, whether participants with one type of pattern presentation are more or less responsive than those with another (Zhang G et al 2004, 2005, He Y et al. 2007). Subsequent trials could use patterns as inclusion criteria or as a means of stratifying trial participants to ensure even distribution between groups. If the intervention given during a trial is individualized (see section 4.6) then patterns should provide the means for differential diagnosis and treatment.

Symptoms & Signs	Pattern differentiation	Treatment principles	Guiding formula “Xiao Yao San”	Individualized formula
Poor appetite Bloating Loose stools Pale tongue	Spleen Qi deficiency	Invigorate the Spleen	Chai Hu Bai Shao	Chai Hu Bai Shao Dang Gui
Dizziness Blurred vision Fatigue Pale tongue Thready pulse	Blood deficiency	Nourish Blood	Dang Gui Bai Zhu Fu Ling Bo He Sheng Jiang	Gou Qi Zi Bai Zhu Fu Ling Chen Pi Yu Jin
Premenstrual tension Temporal Headaches Wiry pulse	Liver Qi stagnation	Harmonise the Liver	Gan Cao	Ju Hua Sheng Jiang Gan Cao

Table 3. Pattern Diagnosis and Treatment in Traditional Chinese Medicine

If the intervention is standardized then it needs to be investigated whether the provision of different treatments according to pattern differentiation have more or less benefit than a one size fits all approach.

4.6 Individualized vs standardized CHM

Much of usual CHM practice involves the administration of individualized prescriptions, based upon the unique presentation of each patient, and the training and clinical experience of the practitioner. This follows the theory of Chinese medicine and is aimed to increase effectiveness and to reduce any adverse effects of treatment.

Using RCT's to research the efficacy of individualized medicines precludes the use of pre-prepared herbal pills or tablets and complicates the use of encapsulated powders. The provision of plausible matching placebos has also been extremely difficult to manage. Individualized treatment also requires the presence of an experienced practitioner to create and adjust each trial participant's formulae, which may be time consuming, expensive, and may reduce the generalisability of the findings from a clinical trial.

Individualized treatments are commonly regarded as best practice (Bensky 1986, Farquhar 1994). Typically when a patient presents a traditional herbal formula is used to provide a basic model for treatment. This is then adjusted to take into account the unique nature of each presentation, the secondary signs and symptoms, and 'constitutional' factors that underpin the health of each person, such as the strength of their digestive system, and their subjective sense of vitality. These subtle changes are considered as important means to enhance the effectiveness of treatment and reduce any unwanted adverse effects. However

there is an increasing trend to use standardized herbal formulae, particularly in clinical research. There is very little hard evidence currently available that compares these two approaches. In one trial for irritable bowel syndrome (Bensoussan 1998) Chinese herbal formulations individually tailored to the patient proved no more effective than standard CHM treatment. However on follow-up 14 weeks after completion of treatment, only the individualized CHM treatment group maintained improvement. This is an important aspect of CHM that requires considerable further research.

In instances where individualized treatments are considered as best practice, research aiming to investigate CHM should try to include individualized treatments within the initial phases of the research process such as observational studies, feasibility trials and pilot trials. If preliminary data using best practice warrants further research it may then be possible to subsequently develop more standardized products to be used during these later investigations. Standardized products, such as pills or encapsulated powders, can be prescribed without a detailed knowledge of CHM theory. They have the advantage of being cheaper than decoctions, and available in a form that could be more readily dispensed within a national health care service.

It is common practice in China and the West for TCM practitioners to prescribe Chinese patent medicine (pills, capsules, tablets) based on pattern differentiation for long-term use, or in instances where the patient either does not comply with the decoction or chooses to take this kind of modern formulation. In these cases, we can still consider this as a form of individualized treatment because these patent medicines are prescribed on the basis of pattern differentiation. However, in China, western medical doctors may also prescribe Chinese patent medicine but on the basis of a more superficial matching of a symptom or disease to a patent remedy, rather than as a result of a more sophisticated pattern differentiation.

4.7 Provision of herbal placebos

Within RCTs placebo controls do not always have to be used. Equivalence trials where CHM can be compared to conventional treatments or to another CHM treatment may be adopted. However the use of a matching placebo allows the identification of the specific effect of a herbal medicine. It may be necessary to conduct placebo-controlled trials to establish a

baseline measure of the efficacy of CHM interventions and that subsequent comparisons be used to assess whether the active intervention is superior or equivalent to other control treatments.

It is relatively easy to match encapsulated herbal powders, or herbal pills using inert starch and colourings, to produce a plausible herbal placebo. Recently the ability to pre-cook herbal decoctions, dispensed as individual dosages in sealed plastic sachets, has facilitated the development of convincing herbal impure placebos with strong taste but no relevant effect on the disease. This plausibility of this methodology has been tested and confirmed (Flower et al 2011). Further work is required to replace the herbs used within the impure placebos with food colourings and flavourings that have a clearly demonstrated and more certain pharmacological inertia.

4.8 Outcomes measures

Most outcomes measures used in WM clinical trials are disease specific and follow the international classification of diseases (ICD). There are different types of measures: objective, subjective and patient centred outcomes. Objective outcome measures such as laboratory parameters are not designed to apprehend the kind of changes in symptoms and signs that are important and meaningful within the framework of CHM. Patient-centred outcome measures that have been designed and validated to assess more complex and subjective changes relevant for the patients and might be more suitable.

The composite indices of different health dimensions (e.g. health assessment questionnaire (HAQ)) have the advantage of providing a basis for combining all relevant end points into a single value. They increase the statistical efficacy of clinical trials by avoiding the issue of p-value adjustments for multiple comparisons thereby reducing the sample size requirements.

The disadvantage is that they often combine outcome and process measures and aggregate items without respect to their relative clinical importance (Bellamy and Buchanan 1993). The use of such indices is recommended even though the different weightings for the individual components in each index remain controversial (Schipper et al. 1990, Bellamy and Buchanan 1993).

It is also important that clinical trials should use (ideally internationally) validated outcomes measures. This makes the findings of these trials more generalisable and facilitates their inclusion within systematic reviews and meta-analyses.

There may be a need to develop new sets of outcome measures that are sensitive to changes that are considered important from the perspective of CHM. For example changes in the colour of a skin lesion or the regularity of the menstrual cycle may be important markers of change to a CHM practitioner. CHM specific outcome measures that are properly validated can be used alongside more conventional measures to ensure that research findings are relevant to the practice of CHM.

4.9 Follow up

Western medicine, in conjunction with the pharmaceutical industry, has developed an astonishing capacity to control the physiological and pathological processes of the body. This may involve killing bacteria, reducing inflammation, suppressing an over-active immune response, or paralysing the gut to stop diarrhoea. Chinese medicine (CM) may start with a similar short term goal (known as treating the branch (Biao 标) but according to traditional theory it is meant to work towards a longer term goal of restoring the diseased system to a state of balanced, sustained good health (known as treating the root (Ben 本)), so that treatment can be withdrawn without a return of the disease state. CM may be slower to act and may require support from the disease suppressing firepower of Western medicine to make an initial impact on a disease process, but its real strength may lay in these longer-term, sustained health benefits. For this reason it is essential that RCT's include follow-up periods

that are long enough (at least one year after cessation of treatment) to assess the therapeutic impact of CHM after the treatment has stopped.

5. Research methodology

This section of the guidelines explores the broad principles of developing a research methodology for a RCT using CHM.

5.1 Literature review

The purpose of a literature review is to find out about existing research to avoid duplication, to learn from any previous successes and mistakes, and to ensure that what is being proposed can be located within the broad traditions of CHM and will therefore have ‘model validity’ (defined as the likelihood that the research has adequately assessed the unique theory and therapeutic context of CHM (Lewith, Jonas & Walach 2002)).

A literature review should ideally incorporate both Chinese and English language sources and should collect both contemporary data and also endeavour to include past records from the canon of CHM medical works. Other language databases can be searched such as Japanese, Korean and German literature depending on available sources.

It is important that, when appropriate, literature reviews attempt to engage with the Chinese language databases such as China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Wanfang Database, Chinese Medical Citation Index (CMCI) and Chinese BioMedical Database (CBM). For searching unpublished studies, the database for dissertations of postgraduate degree in Chinese will be a helpful resource.

There are currently over 17,000 RCT's published in Chinese medical journals (Tang et al 1999, Wu et al 2007). Whilst these generally are of a poor methodological quality they can be used to explore the clinical decision making of experienced Chinese doctors. This can be used to define diagnostic parameters, establish treatment principles, and provide useful data on the selection and dosage of key herbal medicines and formulae. In the past few years the quality of CHM clinical trials has shown signs of improvement with greater transparency and improved methodological rigour. If sufficient trials of reasonable quality are available then a systematic review and possibly a meta-analysis should be considered.

In addition to data from RCT's the CHM journals also contain case histories and case series often from very senior CHM physicians. Whilst these data cannot be included in any statistical analysis these reports can be reported in a review and may be helpful in the development of the herbal protocol for the trial.

Some CHM research is reported in English language medical journals. In addition abstracts of some CHM research are available from the main English language medical databases and it is possible to access translations of the full text from the Chinese journals such as the Journal of Traditional Chinese Medicine (English version) and the Chinese Journal of Integrative Medicine. The Centre for Evidence-Based Chinese Medicine, which is the Cochrane sub-branch of the Complementary and Alternative Medicine Field in Beijing University of Chinese Medicine, is in charge of developing an English database for clinical

trials on CHM published in Chinese literature. Full text translations of Chinese literature can be accessed via this centre in Beijing (Jianping Liu, email: jianping_l@hotmail.com).

Data from classical Chinese texts can provide important insights into traditional concepts relating to the pathophysiology and treatment of disease. These can deepen understanding and ensure model validity in contemporary research. There are an increasing number of these classical texts that are being translated however most are still only available in East Asian languages.

The barrier of the Chinese (and other East Asian languages) provides a serious obstacle for any attempt at a genuine systematic review of CHM literature. However it is a barrier that needs to be overcome. There are two options for non-Chinese speakers. The first is to learn to read medical Chinese. The second, less arduous option, is to collaborate with Chinese speaking researchers either in the West or within China.

5.2 Trial phases in conventional drug research

The randomized controlled trial process was designed around testing the efficacy of drugs rather than for use in surgical or manual interventions such as physiotherapy or osteopathy, or complex interventions such as CHM. Clinical research in drug development can be divided into four main phases (Phase I, II, III & IV trials) which represent vital progressive steps in testing the safety and efficacy of modern pharmaceutical agents.

In pharmaceutical development, before clinical trial is launched there will have been many years of very careful testing carried out both ‘in vivo’ and ‘in vitro’ to minimize the risk to humans of taking a particular drug and to maximize the potential therapeutic benefit. The primary aim of these studies is to assess the Absorption of a drug, its Distribution through the body, the effect on Metabolism and the extent of Excretion – collectively known as the ADME of a drug.

In *Phase I* clinical trials are usually carried out in healthy individuals who do not have a pre-existing pathology. The aim of these studies is two-fold:

- To establish safety data e.g. on the maximum tolerated dose by very cautiously increasing the dose of the medication in patients and to look for side effects.
- To assess whether the medication has an effect on the healthy individuals

The criteria used to define the ‘maximum tolerated dose’ and ‘specific effect’ varies significantly depending on the illness. For instance, patients with terminal cancer may give consent to a trial even if there are uncomfortable side effects because they wish to help future patients or because they believe the drug will be effective. This is less likely in the case of patients with an intermittent benign illness such as migraine.

Phase II studies are carried out in patients with a known illness and usually involve four treatment groups recruited to a prospective randomized clinical trial. While a Phase I study may estimate the likely doses of a potential therapeutic agent, a Phase II study carries this work further, usually looking at a number of different therapeutic doses in different arms of the trial-usually with a placebo as an additional comparison. With most conventional pharmaceutical agents, therapeutic benefit increases with the size of the dose, but so does the potential risk of adverse reactions. The aim is to find a dose that provides the best clinical effect with the lowest level of adverse reaction. Typically, in one arm of the trial patients will receive what is thought to be the therapeutic dose; a second arm will be given half that dose and a third arm double the optimal dose, while the fourth arm receives a placebo. The specific treatment efficacy will be evaluated by comparing the balance of therapeutic benefit and adverse reaction with the active agent versus a placebo. In CHM research in China the Chinese regulation authority for approval of new herbal drugs (the SFDA) requires all herbal medicines to go through phase II and III trials, and encourages the use of placebos as a control in phase II trials. Up until 2008, more than 9000 Chinese patent medicines were given market approval in China by SFDA (<http://www.satcm.gov.cn/zyxw/20080721/101217.shtml>).

A *Phase III* clinical trial mirrors most closely the typical RCT. It is a study that involves two or more groups (arms) and compares the optimal dose of active treatment with a placebo, comparable treatment, or a waiting list control group, over a period of time and uses outcome

measures that will allow researchers to conclude that any effects observed will be the specific effect of the drug or intervention being evaluated.

A common trial design used within a Phase III RCT involves a two armed comparative designed to evaluate the difference between a specific intervention and a placebo or control intervention with clearly defined primary and secondary outcomes. In some instances, particularly for chronic conditions, various adaptations on this basic design may be applied. For instance, a run-in period may be used to establish baseline symptoms prior to trial entry. This allows for the general improvement that may occur as a 'trial effect' will become apparent as patients record their symptoms over a period of a week or a month (Lewith *et al.* 2002; White *et al.* 2004). It may also be used to exclude participants who present with very minor symptoms that would be insufficient to demonstrate clinical improvement occurring as a consequence of the intervention.

Phase IV clinical trials (also known as a Post Marketing Surveillance studies) are conducted after a drug has received a license and is being prescribed in routine clinical practice. A Phase IV trial is initiated to screen for any short or long-term adverse effects and to evaluate the 'real world' effectiveness of an intervention outside the highly controlled confines of a RCT. Based on the research question these trials can be randomized or prospective observational studies. Depending on the regulation in different countries, it might be possible that research exploring existing practice of CHM is considered as Phase IV research whilst interventions using novel formulations or seeking to obtain a full drug license for a CHM product will be required to fulfil the requirements of all the standard research phases. This should include a post-marketing phase to ensure safety once the product is used in a larger population and over longer periods of time than are normally possible in earlier phases of research.

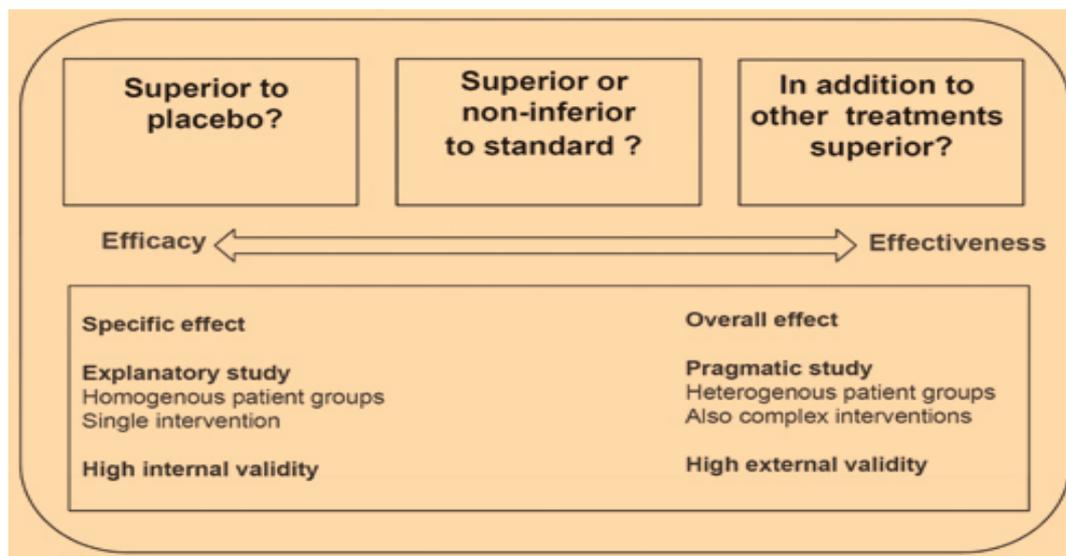
For clinical research of existing practice, not for novel herbal product development, phase III and IV trials are preferred to explore the effectiveness and adverse effects. The study design should be specifically designed according to the research questions and objectives.

5.3 Randomized study design options

There are several design options:

1. *The explanatory RCT* is designed to control for all potential confounders to enable an accurate assessment of the specific effects of the experimental intervention in relation to an inert (placebo) or a well evaluated control. The advantages of this approach are that it allows an assessment of the causal efficacy of a specific intervention. The disadvantages are that this design may be poorly suited to evaluate complex interventions using individualized treatments that derive therapeutic benefit from a combination of specific and contextual factors. Explanatory RCT's also frequently test a single remedy on a highly selected homogenous sample population under ideal conditions. This may not be generaliseable to 'real world' practice.
2. *The pragmatic clinical trial (PCT)* is less tightly controlled than the explanatory RCT and does not try to exclude the contextual effects of treatment. It is designed to test the effectiveness of a treatment in a real world setting with a heterogeneous population using patients-centred outcomes as endpoints. It is a less internally rigorous design that cannot establish the causal efficacy of a specific aspect of treatment but it has greater external validity and generaliseability than the explanatory RCT (see Fig 1).

Fig. 1. The relationship between the research question and the corresponding study design



3. *A cross-over trial* is a study that assigns participants into one treatment or placebo in random order in a first phase, followed by a washout period with no treatment, and then a second randomized treatment with a control group in a further phase. Every individual takes part in both phases, but the order of treatments is randomized. The advantage of a cross-over design is that it minimizes variation. Each individual becomes their own control and so the inter-individual variation is minimized, and thus smaller numbers are needed. Cross-over designs are only appropriate for a stable disease and a therapy that has relatively short-term effects. As CHM may have long term effects it is a design that may not be appropriate for CHM research although there have been some very successful trials using CHM for atopic eczema using this design (Sheehan et al 1992).

4. *The N-of-1 trial* can be performed as of cross over trial involving only one patient. There are a number of different methods for using N-of-1 trials. A common format involves the participant being initially randomized to either treatment A or to treatment B. After a period of treatment they are then switched to the other intervention which may be an active treatment or a placebo control. This can occur on several occasions to confirm the effect of a specific intervention, so the effects of the intervention can then be assessed. This approach could represent a way to make the traditional use of a case history more rigorous and scientifically acceptable. N-of-1

studies can be used to help to assess individual rather than group responses to treatment and may also investigate mediators of a therapeutic change such as herb selection and dosage. However the data is only very weakly generalisable to other patients and carry over effects from one phase of the intervention may be an important confounding factor.

There are several other ways in which a randomized study may be modified or combined to provide different types information. These include:

a) **Mixed methods design (Cresswell 2003).**

This involves the use of qualitative research methods in addition to quantitative outcomes measures. Qualitative research provides a deeper, more patient centred, account of a participant's experience during the clinical trial. It can help to clarify the impact of an intervention and generate new hypotheses that may be tested in subsequent study.

For example, a randomised trial using qualitative research to investigate the knowledge, attitude and expectations of participants towards the tested treatment could use a subgroup analysis to examine the impact of high expectation versus low expectation on the treatment outcomes. The relationship between treatment effects and social/behavioural factors are contextual influences that can then be included in the explanation of the trial findings.

A second example is the use of qualitative research methods to analyze cancer patients' experiences, attitudes and beliefs in relation to CM. This would complement the use of quantitative outcomes measures that can only capture a relatively narrow range of patient experience. A pilot study undertaken in China (Xu et al 2006) revealed that Chinese cancer patients were willing to receive CM because it appeared to improve their quality of life; they trusted CM because of its long cultural and historical tradition; and they wished to use it as a long-term treatment option. Without qualitative research this subjective information would not be taken into consideration.

Qualitative research also has an essential role as a methodology to investigate the various processes that underlie the complex nature of CHM. It will help in the development of models to describe and explain CHM intervention, and conforms to the recommendations made within the MRC guidelines for complex interventions. Understanding these qualitative data will help CHM practitioners improve their service delivery, and will contribute towards defining key aspects of CHM, such as the use of pattern differentiation or individualised treatment programmes, which could be incorporated in quantitative research projects. These data will also help to explain what CHM is and how it works to interested parties, who do not have a specialist knowledge of CHM, and may clarify aspects of CHM that could be transferred to other medical traditions.

Examples of the kinds of questions that could be addressed by qualitative methods can be seen in Table 4.

Table 4. Qualitative research questions in CHM

Research question	Methods of data collecting	Methods of data analysing
What is the patient's and CHM practitioners' experience, knowledge, attitudes and barriers of taking CHM? (Xu et al 2006)	Interviews; focus group; (Marks and Yardley 2004)	framework analysis; thematic analysis; Grounded theory (Green & Thorogood 2004);
What is the whole consultation between CHM practitioners and patients? And how does it happen? (Yu et al 2010)	participant observation; non-participant observation; interview (Yu & Liu 2008)	conversation analysis; thematic analysis; (Liu 2009)

b) Multi-factorial trials.

It is generally the case that it is preferable to answer one research question at a time. However, sometimes it will be important to ask more than one question. Factorial designs provide an excellent and efficient framework for asking several questions simultaneously. The statistical calculations associated with this design mean that a number of questions can be asked with slightly fewer trial participants. Inevitably multi-factorial studies are

complex, difficult to execute, and require considerable research expertise. An example of a multi-factorial trial could be a placebo controlled trial comparing equal groups using individualised and standardised treatments employing either decocted or encapsulated, verum and placebo forms of CHM. This would enable a comparison of:

- Decoctions vs placebo decoction
- Encapsulated powders vs placebo powders
- Individualised decoctions vs uniform non-individualised decoctions
- Individualised encapsulated herbs vs uniform non-individualised encapsulated herbs
- Uniform non-individualised decoctions vs uniform non-individualised encapsulated powders
- Individualised decoctions vs individualised encapsulated powders.

These data are extremely important to test basic assumptions about the modes of administering CHM. However the power of this kind of trial to detect fundamental differences between CHM and placebo treatment is reduced and larger numbers of participants would have to be recruited as a result.

Factorial trials have been suggested as an effective and cost-effective way of adding in one or more interventions into an existing phase 3 trial. As such Pocock (1979) has described it as considerably underused facility. For TCM trials they may offer a way forward for situations where funding for the primary trial is difficult to obtain for the herbal product but may be more readily available for a pharmacological product.

Factorial trials, particularly for Western based drug trials (e.g. Logan et al 2008), are more commonly being applied recently as their advantages are being more widely recognised and they potentially offer a very useful approach for the evaluation of herbal products that do not interact with drug that is “sponsoring” the trial.

Examples of factorial trials of natural and herbal products include evaluating garlic for its effects on early gastric pre-cancerous lesions (Gail and You 2006).

c) Cluster trials.

In cluster, randomized trials relatively discrete groups are randomized before participating in a trial (e.g. randomization of GP practices or clinic wards). They are useful when randomization of individual patients is not possible or desirable, such as in situations where members of a control group could be contaminated by exposure to the experimental intervention. In CHM research this approach could be used to disguise differences in taste between verum and placebo herbal medicines that could undermine participant blinding.

d) Expertise based RCT's

Expertise-based randomised trials randomize participants to clinicians with expertise in intervention A or clinicians with expertise in intervention B, and the clinicians perform follow the approach they are expert in. This could be a way of testing the relative effectiveness of different traditions within CHM (Devereaux et al 2006).

e) Adaptive Trials (Muller and Schaffer 2001)

Adaptive trials are a further growing trend in drug-based trials as again they offer potential for maximising the informative output from a clinical trial. Conventional clinical trials, being based on “frequentist” school of statistical theory, effectively start by assuming that nothing is known and new data is collected to either accept or refute the “null hypothesis”. As such they can appear “wasteful” if the intervention does not show evidence of effect, even if the intervention “failed” on the trial power alone, in that further trials also have to start from a similar null hypothesis. Adaptive trials allow inclusion of options for sample size re-estimation, response adaptive randomisation, and “drop-the-loser“ intervention as considered further below:

1. Sample size re-estimation allows the trial designers at the outset to set parameters for modifying the sample size requirement to be monitored and adjusted in the light of early trial data without compromising the overall integrity of the trial. As such it avoids the common pitfall of many trials being underpowered from the outset and can be particularly useful if combined with other adaptive trial option below.

2. Response adaptive randomisation allows for modifications to be made to reduce the number of patients that are assigned to the inferior treatment arm. Some argue that this is not in keeping with true “full” randomisation in that the allocation to active or placebo arm should be completely random and not changing throughout the duration of the trial. This theoretical and ethical point of view can however be offset by inclusion of formal stopping rules with the trial design set at the outset.
3. “Dropping the loser” or “picking the winner” refers to the practice of removing allocation groups based on formally defined decision rules and is especially useful in phase 2 trials in choosing/deciding between different dose levels.

Adaptive trial designs are the focus of a lot of further development work in clinical trial academic groups and potentially offer a more productive way forward for Chinese herbal product trials, as they help more quickly and effectively to identify active products (Chow & Chang 2008, Cirulli 2011).

Adaptive trial designs could be used for looking at the “whole systems” approach of CM.

f) Health economic studies

Clinical studies are increasingly used to assess the economic implications of the intervention being tested. In addition to outcomes data, cost data has to be made available from a trial. The most common health economic analyses are the cost of disease analyses, which compares the costs between both groups, and cost-effectiveness analyses, which calculates the ratio for the additional benefit in relation to the additional costs. In a cost-effectiveness analysis benefit is measured using naturalistic units, for example, costs per mmHg lowered systolic blood pressure, or costs per 10mm reduction on a visual Analogue Pain Scale. The cost-utility analysis is subcategory of the cost-effectiveness analysis and uses quality adjusted life years (QALYs) as outcome measures. Beside other methods (e.g. time-trade off, standard gamble) there are a number of internationally validated measures that can be used to calculate QALYs (e.g. SF-36, SF-12 and EQ-5D). If the intervention is superior in terms of benefit compared to the control but has higher costs, then a cost-effectiveness analysis is required.

5.4 Blinded or open trials

Open studies, when both participants and investigators are aware of the nature of the treatment, are easier to organize than single or double-blinded trials. However the outcomes of open trials are more easily biased by participant, researcher and assessors beliefs when compared to blinded trials.

Blinding aims to remove bias, retain patient and assessor equipoise (i.e. participants and those evaluating the data from the trial do not have a preference for one treatment above another). It is used to detect the specific effects of an intervention by making any prior 'expectation' that the researcher or participant may have of the trial results from the active or placebo treatment the same for both groups. It is usually possible to blind a medicinal intervention. A placebo can almost always be made to look, taste, feel and present as indistinguishable from the active treatment. However, blinding with respect to CHM is more difficult. If pills or encapsulated concentrated herbal powders or granules are used then the development of an inert placebo is relatively straightforward. However, as described earlier, placebo controls for decoctions are more problematic. Nevertheless it is now possible and practical to conduct double-blinded placebo controlled trials using herbal decoctions.

In a double-blind trial both the therapist and the trial participants (volunteers/patients) are unaware whether they are receiving or delivering active or placebo treatment. Because both parties are randomized to the treatment and are blind to the nature of the intervention their expectation should not affect the differences in outcome between both groups. In addition blinding those processing data from the trial is also important to ensure an unbiased assessment.

A single-blind trial is where the therapist delivering the intervention knows which is the placebo and which is the active treatment, but the patient or volunteer does not know which group he has been randomized to.

It has been estimated that approximately 70 per cent of clinical trials fail to report the details of blinding (Schulz & Grimes 2002) . Schultz argues that the removal of bias is the foundation upon which causal associations can be derived within clinical research. He points

out that many conventional clinical trials fail to report the blinding (and randomization) process adequately and how successfully this was maintained during the trial. In some instances researchers may have deliberately subverted this process (Grimes & Schulz 2002). However, it is possible to minimize the effect of open (unblinded) interventions by generating a placebo effect in each group, using the process of a supportive consultation by the therapist/physician to enhance the contextual effects of the intervention. For example, in an open pragmatic trial comparing prescribing strategies for a sore throat, where the placebo effect of prescribing antibiotics was minimised as a confounding issue by using structured and supportive advice sheets to support management in each group, with the added possibility of a delayed antibiotic prescription. This minimises the need for an immediate prescription of antibiotics simultaneously enhancing the non-specific effect of the intervention (Little *et al.* 1997).

When carrying out a trial, researchers should aim to detach themselves from pre-conceptions about the efficacy of a therapy to achieve equipoise. However in research where a practitioner is investigating the system of medicine that they have studied, practice and 'believe in' this may not be possible. In these instances whilst blinding helps prevent bias it may also introduce a new bias by undermining the normal conviction and confidence of the practitioner that may be an important component in the overall effect of the treatment. A paper written by a group of complementary therapists exploring the tension between being a practitioner and a researcher observed: "Patients want the credibility, confidence, intention, conviction and belief in our particular therapies and this is critical to being an effective practitioner. How can we provide this when we have doubt?" (Lewith *et al* 2009).

Despite these tensions, blinding is particularly essential during the data interpretation. Ensuring assessor blinding, at least in the preliminary stages of data evaluation, helps to ensure more rigorous research.

5.5 Taking patient expectation into account

Patient preferences and patient expectation can play a role in trials on CHM. Randomisation could have a direct impact on the selection of participants. For example, if preferences have a

significant influence on whether patients choose to participate in a study and whether they respond to treatment, the findings of randomized studies may not apply to those patients who avoid participating in trials. Two systematic reviews suggest that the influence of patient expectations on outcomes might be related to both for within-group changes and between-group differences (Crow et al 1999, Mondloch, Cole & Frank 2001). This has already been shown for acupuncture (Linde & Witt 2007) and is likely to be true for CHM. If the patients in a CHM trial have higher expectations of a positive outcome than the ‘average’ patient then this could result in within-group changes that are larger than those of a more representative sample. High expectations might also be associated with high response rates and improved outcomes in the placebo control group. This could result in a ceiling effect, making it more difficult to detect a significant difference between active and placebo interventions. There are different methods to deal with the problem, such as: a run in phase, stratification for randomization and measuring expectation. A simple tool (for example Devilly and Borkevic 2000) can measure aspects of expectations at baseline by asking questions such as: “How effective do you consider the treatment in general?” with responses such as “very effective, effective, slightly effective, not effective, don’t know”. These data could be used for adjustment in the primary data analysis.

5.6 Randomization and related issues

Randomization is one of the most important ways of removing confounding within a RCT. The initial aim is to ensure that baseline factors of each group are equally distributed to avoid confounders that may independently predict outcome occurring more often in one of the groups. Allocation concealment should separate whoever generates the randomization codes from the person carrying out the randomization, to minimize any possibility that the clinician managing the patient could have any influence on the choice of group. In a placebo-controlled trial this can be accomplished by an independent pharmacy making up randomization packs containing active drug or placebo, and for an open trial this is best accomplished using an external telephone randomization line.

5.6.1 Clustering

Randomization in multi-centre trials can present a variety of different problems. The same treatments may not be delivered in the same way at every centre, or treatments may be delivered at some centres and not others so the outcomes found might be centre dependent with treatment effects ‘clustered’ in consequence. Every effort should be made to standardize for recruitment, sample size and any analysis should allow for possible clustering. It is possible to consider each practitioner involved in the research as a ‘centre’ of treatment and to apply a statistical analysis to evaluate the magnitude of the effect of different practitioners on the outcomes of the trial. Those interested in understanding and accounting for the effects of clustering in the analysis of a multi-centre trials should refer to Campbell and Machin (1999).

5.6.2 Mendelian Randomisation

Mendelian randomisation refers to the use of the variation that exists between individuals in terms of their genetic make-up. Where this potentially has usefulness for “clinical trials” is that it can be seen to effectively “randomly” allocate the internal dose of a product on the basis that even in two individuals who take the same external dose, if one has a genetically determined (and hence easily measurable) metabolically different ability to excrete ingested drugs/products then the effective dose will be different to another individual who cannot excrete the ingested compound so well. Furthermore, as this ability is unknown to the individuals themselves then it effectively randomises the allocation of active agent (Smith & Ebrahim 2003, Bennett 2010). This apparently theoretical observation appears to actually have potential utility, particularly for plant based products, in that humans have marked inter-individual variability to excrete such products. This is thought to be derived from an evolutionary perspective, as man has always had to deal with ingested plants, many of which are potentially toxic.

Limitations to the approach, however, currently centre on our incomplete understanding on the full pathways that regulate internal dose, as current understanding is principally based on predicting the outcomes on the basis of the cytochrome p450 and n-acetyl-transferase systems interactions alone. As such this does have implications for the future of so-called

personalised medicine, and does potentially offer up the hope of undertaking comparison of groups “randomly” taking different effective doses, even in cohort/follow-up studies without formal randomisation. However few examples of where this approach has been effectively used are available yet, and it is extremely unlikely to ever replace formal randomised clinical trials per se but may yet help in selecting agents showing a further level of evidence of effectiveness.

Further examples of where this approach is starting to show its potential can be found in the following articles (Allin et al 2010, Chen et al 2008, Davey-Smith 2007, Kamstrup et al 2009, Wang et al 2011).

5.7 Stratification

In small single centre clinical trials, great attention must be paid to understanding both the illness and the effect of interventions, along with potential predictive factors that may independently influence treatment outcome. This is because, for very large trials, confounders will be usually equally distributed between groups. For smaller trials, particularly where some variables strongly predict outcome, it is important to make sure that such variables are balanced between groups by ‘stratification’. In addition in multi-centre trials the single centres are often separate strata. Since patients included in a study as well as their prognoses might vary in different practices or hospitals, it is important that similar numbers of patients are allocated to the experimental treatment or to the control condition in each study centre.

Another reason for stratification is to balance patients in subgroups to allow useful subgroup analysis, for example, for different TCM pattern diagnoses. This would enable an assessment of which TCM sub-types may be more or less responsive to treatment than others, which would be useful data for analysing the trial and in preparing for any future related research. This trial design allows an individual CHM treatment according to the CHM diagnosis. In this type of trial, the patients should not only be blinded for the treatment but they should also receive no information about their CHM diagnosis.

A potential problem with this approach is that different patterns would result in a larger number of subgroups and most of them will be too small to have enough statistical power for a subgroup analysis. Because of this it may be necessary to pool similar patterns, or patterns commonly occurring together, for the primary analysis and to only use pre-specified subgroup analysis for the more common patterns.

5.8 Measuring outcomes

It is important to specify a primary outcome in a research study so that a type I error (ie false positive results due to chance findings), can be avoided. (For example, if 20 outcomes measures were used in one clinical trial, it is likely that one of these would show a significant difference between an active and placebo treatment at the 5 per cent level (that is, 1:20 times), and consequently this might be considered a significant outcome. It is, in fact, likely to be simply a random event if all the other 19 outcomes show no difference between the active and the placebo treatment. To counter this random event a pre-determined primary outcome is stipulated.). The choice of primary outcome will be determined by the type of trial: thus in a pragmatic trial where the beliefs and behaviour of the participants behave as naturally as possible, with minimal interference, then patient-centred outcomes may be developed for use, rather than objective measurement of outcomes by independent observers.

It is also important to consider, measure and control, any factors known to predict or confound an outcome. For example, if patients are receiving either CHM or physiotherapy for their back pain, then outcomes may be predicted by the attitudes and beliefs that trial participants hold about a particular intervention. If possible, these attitudes should be established in the feasibility stages of the study.

Ideally, as for all research using quantitative outcomes measure, the outcomes in CHM should be measured independently of the investigator and if possible using an assessor blind to the group (ie unaware of which participant is allocated to which group) to minimize outcome assessment bias. Outcomes should also be measured in the same way in each group to avoid bias as the manner and timing of a measurement may affect that measurement.

6. Legal considerations

In the EU the administration of CHM for research purposes constitutes a Clinical Trial of an Investigational Medicinal Product (CTIMP) and is therefore covered by the EU Clinical Trials Directive (2001/20/EC) and the relevant legislation in the member states. In the UK CHM research is subject to the Medicines for Human Use (Clinical trials) Regulations 2004 as therefore requires a Clinical Trials Authorisation (CTA) from the regulatory body. In the UK the CTA is obtained from the Medicines and Health Care products Agency (MHRA).

Technically the manufacture or importation of an IMP requires an appropriate Manufacturing Authorisation (MA's). However at present, in the UK at least, no herbal supplier has MA status for the supply of CHM. In the past, when using dried herbal or granules within the UK, the Approved Suppliers Scheme set up by the Register of Chinese Herbal Medicine has been used as a surrogate for MA. However encapsulated concentrated powders/granules are considered as a finished herbal product that must be imported by a company who holds a licence to import clinical trial materials. This company will provide the necessary data and ensure the correct checks in place to ensure that the manufacturer has EU GMP certification, or equivalent standards of GMP (at present from the US or Australia). This along with available data on the chemistry and toxicology of the herbal product will allow the MHRA to consider the herb as an Investigational Medicinal Product (IMP) and therefore should allow the MHRA to approve herbs for the purposes of a clinical trial. Such a product will also be exempt from the EU licensing requirements recently outlined for herbal products in the Traditional Herbal Medicine Products (THMPD)

All clinical trials in the EU also require a Research Sponsor to take overall responsibility for the study, who has provided adequate indemnity and has sufficient infrastructure to have sufficient oversight of the study and satisfy the regulatory body for each member state. A clear account of the arrangements for providing cover for negligent and non-negligent harm will be required before a clinical trial can be reviewed by a legally constituted Research Ethics Committee, provided with a favourable opinion and eventually authorised by the MHRA and hosting organisation (an NHS Trust, University or private clinic).

The legislation requires an Investigators Brochure to be held containing all the legal and ethical documentation relating to the authorisation of a clinical trial. An example can be seen in the European Medicines Agency Clinical Trial Guidelines document available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

6.1 Legal requirements in the EU

It is outside of the remit of this document to provide in depth information on all of the legal requirements for clinical trials in the EU or China. It is necessary for anyone intending to conduct a clinical trial into CHM to familiarise themselves with the appropriate regulations in the country where the study will be hosted.

In the EU information and forms are available at

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm for

requirements such as:

- Applying for clinical trial authorisation
- Obtaining ethical approval
- Registering with the European Clinical Trial Database (EUDRACT)
- Monitoring and reporting adverse reactions
- Requirements for Good Manufacturing Practice (GMP)
- Requirements for Good Clinical Practice
- Requirements for Good (Clinical) Laboratory Practice

Individual host countries will have their own legal requirements for clinical trial authorisation and their own procedures for obtaining ethical and approval from the hosting organisation.

6.2 Legal requirements in China

In China, the State Food and Drug Administration (SFDA) has issued Good Clinical Practice (GCP) guidelines (<http://www.csc.org.cn/gcp/>) which required all new drugs including CHM herbal drugs to be registered and granted a Manufacturing Authorisation before clinical

trials on humans can commence. Prior to this GLP (Good Laboratory Practice) is also required to subject drug-herb IMPs to in vivo tests in animals and in vitro pharmacological and toxicological tests prior to a phase I clinical trial. Once these safety measures have been completed the SFDA can approve the IMP for clinical trials (phase II and III).(<http://www.sda.gov.cn/WS01/CL0053/24473.html>)

In January 2007, the Chinese Ministry of Health issued ‘Regulations on ethical approval concerning biomedical research in humans’ relating to clinical trials investigating new drugs, new biological products, new vaccines, new surgery, new medical equipment or techniques, which became the first official document in China to require ethical approval for any research on humans. See:

<http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohkjjys/s3581/200804/18816.htm>

After this initiative, many Chinese institutions and organisations have established ethical review committees (ERC) or institutional review boards (IRB) to approve clinical research in humans including healthy volunteers and patients. However, these regulations do not cover clinical trials on traditional herbal formulae or observational studies on practitioners’ experience. Therefore, a large number of trials on CHM in China are still outside of this regulation.

7. Ethical considerations and trial registration

In the EU all clinical trials conducted in tertiary education and within the mainstream health services are subject to review by an independent ethical committee and are registered in the EU clinical trials database EUDRACT (European Union Drug Regulating Authorities Clinical Trials). We consider that all clinical research, however small the study might be, requires ethics approval and informed consent and should be registered in an open access registry such as that recently launched by the UK National Health Service (NHS) which involves an open-access [NHS Trusts Clinical Trials Register](#), which assigns a unique International Standard Randomised Controlled Trial Number ([ISRCTN](#)) to each randomized, controlled trial funded by the NHS. The ISRCTN will help researchers track the publications

that result from a given trial. Ethical approval should be consistent with the prevailing national legislation in country where the patients are being recruiting into the study.

Clinical trials conducted by researchers operating outside of the auspices of mainstream health or education services will still be required to meet the ethical requirements set by their professional body. They will also be required to obtain approval from the government body set up to regulate clinical trials (in the UK this is the MHRA).

In China, only new drugs need to be approved by either the ERC or IRB. Clinical trials outside of this category are not covered by statutory regulation. However in instances of government-funded research the institutions and organizations will request for ethical approval from their ERC or IRB even there is no official requirement to do so. The authors of this paper consider it essential that any clinical trial involving human (or animal) subjects should obtain national ethical approval.

8. Protocol development

The guidelines in this document relate to the general principles of writing a clinical trial protocol. The specific structure of a protocol will vary according to local and national requirements. Detailed examples of different national guidelines can be down loaded directly from the internet. In the UK for example these are available from:

<http://www.suht.nhs.uk/media/suhtinternet/randd/information sheets/is3aguidetowritingaprotocolfortimp.pdf>

For other EU countries, Japan and the United states see the ICH good clinical practice guidelines available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002874.pdf

A protocol is a document that describes the background and rationale for the trial; it identifies the trial objectives of a trial and describes how the selected design, methodology (including

statistical analysis) and organization will achieve these ends. It includes details relating to the governance of the trial such as recruitment, informed consent, legal and ethical obligations and safety considerations i.e. pharmacovigilance and the reporting of any adverse events. The protocol should evolve from an iterative process involving a team of researchers, practitioners, statisticians and patient group representatives. The protocol should include the following:

8.1. General Information

- The title of the clinical study.
- Names (titles), roles and contact details of key personnel including sponsors, Chief and other investigators, and details of the various sites used during the trial.
- List of abbreviations and definitions

8.2. Hypothesis and Null Hypothesis

The design of a research project will be fundamentally governed by the primary hypothesis, or the proposition to be tested. A clear statement must be made of the hypothesis that the trial is testing and the null hypothesis that the trial is trying to disprove. This can be briefly stated but must be *firmly* based on the research question(s), and is frequently a null hypothesis – that is a proposition that suggests that statistically it is unlikely that the treatment will be shown to have an effect (see Chapter 11 on statistics). A Phase III clinical trial will inevitably have one main hypothesis, although there will almost certainly be a number of secondary research questions.

8.3. Trial objectives

A clear statement of the objectives and purpose of the study is required.

8.4. Trial justification

The justification of the proposed study based on the available information including a consideration of the data on the subject from modern as well as traditional literature, pilot

studies and previous clinical experience.

8.5. Site details

Details should be provided relating to the site and the facilities where studies will be undertaken. Details such as disabled access, public liability insurance and reception cover are required.

8.6. The trial design

Including the choice of:

- Blinding or open designs (see section 5.4)
- Randomization and related issues (see section 5.6)
- Stratification (see section 5.7)
- 6.2.2 Clustering (see section 5.8)

8.7. Inclusion and Exclusion criteria

It is recommended that the primary inclusion criteria relate to biomedical disease categories (which could then be sub divided according to TCM syndromes). This ensures that the research is relevant to the wider, non-TCM literate research community and it also facilitates the pooling of data for systematic reviews and metanalysis.

CHM diagnosis could be used as additional inclusion criteria to recruit only those patients with the relevant CHM diagnosis for the researched formula. When using this design, it must be recognized that a large number of patients may need to be screened. In addition, the results are less representative for the Western diagnosis and integration into conventional care might be more difficult, because Western trained health care providers could not differentiate between the different CHM diagnoses, unless a practical diagnostic algorithm to enable simple syndrome differentiation was developed and validated.

8.8. Trial numbers

The number of study subjects needed to achieve the study objective, ideally based on an appropriate power calculation and taking into account an estimate of drop out rates. Details should also be provided relating to how patients will be approached and recruited for the trial and any anticipated difficulties and potential biases that may result from the recruitment strategy (for example recruiting from self help groups might result in a more recalcitrant sample population than recruiting from a hospital patient list).

8.9. Outcome measures (see section 4.8)

These include the subjective and objective clinical observations and laboratory tests which will be recorded during the course of the study together with a rationale explaining why they were selected, how they will be used during the trial, and what constitutes a clinically important change. It is important that, where possible, outcomes measures are (ideally internationally) validated. It is also desirable that CHM and TCM specific outcomes measures are developed and validated (see section 4.6).

8.10. Data related to herbal medicines

This should be in accordance with the latest herbal CONSORT guidelines for clinical trials involving herbal medicines <<http://www.consort-statement.org/extensions/interventions/>>

These data should include:

- a rationale for the range of herbs to be used in the study together with any pharmacological data supporting this view. Information relating to toxicity (eg LD50) or herb-drug interactions should also be provided. Guidelines on the assessment of genotoxicity of herbal substances/preparations have been published in 2008 (EMEA/HMPC/107079/2007). In order to reduce testing a test strategy has been developed and published (EMEA/HMPC/67644/2009). A recent overview is given by Kelber et al (2011). Some type of biochemical profile of the herbal preparations should be provided to safeguard reproducibility. In case of unknown bioactive

compounds, a qualitative HPLC-fingerprint analysis may be used. In case of known bioactive compounds, quantitative assessment should be carried out. A unique marker substance of the herbal preparation can also be included.

- Details of where the herbs are sourced from, and how they are stored, and dispensed. A supplier should meet agreed standards of good manufacturing practice (GMP) and good agricultural practice (GAP).
- Herbs should be described using both pin yin and scientific Latin binomial names (as defined by the International Code of BN (<http://ibot.sav.sk/icbn/main.htm>) that identifies the genus and species of the herb with the author of the classification, the plant part, and any method of processing used. These standards should be adopted for all CHM related research. Thus the Chinese herb Dang Gui (当归) should also be identified as *Angelica sinensis radix* (OLIV.) DIELS. . Voucher specimens should be kept for later reference.
- Details need to be provided on how the herbs will be prepared (eg tablets/ capsules/ decoctions including the cut size of the material, cooking times and temperature, biochemical profiles); how they will be administered (eg orally, externally, intravenously, or via a herbal enema); and what dosage will be given during the trial.
- Biodiversity rights for the herbs used in the studies should be followed.

8.11. Adverse events

Recording of adverse reactions and Serious Adverse Events (SAE) should conform to current EU guidelines that can be downloaded in full at:

http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_294/l_29420061025en00320050.pdf

For trials relating to CHM an example of a SAE document has been included in Appendix *. An adverse events committee should also be convened in the event of a suspected SAE ideally comprising, in the instance of CHM, of a herbal practitioner, a conventional medic, a toxicologist, and a statistician.

8.12. Control groups

In CHM there are a number of different options for controls to be used during the trial as a comparison to the active treatment under investigation. These include:

- Placebo control
- Conventional treatment control (e.g. standard treatment, usual care)
- A different CHM regime
- Waiting list control group (no treatment)

The choice of control group will depend upon the aims of the study. A trial aiming to estimate the specific and contextual effects of treatment for example might include an active group, a placebo control and a waiting list control group. Comparing active and placebo treatments relates to the specific effects whilst a comparison of placebo and waiting list groups allows an estimation of the contextual effects of an intervention.

8.13. Treatment schedule

To include treatment period and time including any run in periods and post treatment follow up.

8.14. Use of other treatments

The criteria for other treatment that may or may not be given to subjects during the study should be clearly described.

8.15. Recording data

The methods of recording responses, methods of measurement, times of measurements and follow-up procedures should be provided a description of the Case Record Forms or equivalent documents (see section 9).

8.16. Evaluation of trial results

The methodology of the evaluation of results (e.g. statistical methods and reports on

patients/participants who withdraw from the study) should be clearly described. This should include an intention to treat analysis that includes all participants who originally enrolled in the trial.

8.17. Participant information and consent

Information to be given to study subjects such as patient information sheet, consent forms, letters to GPs etc. An example of guidelines for these documents can be seen at:

<http://www.suht.soton.ac.uk/researchpack/SectionD/Ethics%20Guidance%20for%20Patient%20Information%20Sheets.PDF> but each country may have different ethical requirements on information that should be provided to trial participants that will be determined by the relevant body regulating national ethics approval.

8.18. Staff information

Copies of documents or details of training given to the staff involved in the study should be clearly described.

8.19. Time schedule

A time schedule for completion of the study should be included.

8.20. Escape treatments

Details should be provided of the medical care to be made available to patients during or after the study that if necessary may override protocol treatment.

8.21. Ethical approval

Ethical considerations and measures relating to the study should be described, including details of the ethics committee, dates of application, required modifications and so on.

8.22. Legal status

An account of the legal status of the trial (as outlined in section 6) and relevant communications with appropriate regulatory authorities should be provided.

8.23. References

To include a full list of literature referred to in the protocol.

9. Case report forms

Case report forms (CRFs) are designed to record data on each trial subject during the course of the trial as defined by the protocol. A CRF for each patient in the study must be completed and signed by the investigator and assessor. All the events that happened in the trial should be fully documented, including adverse reactions.

10. Data management

Trial data should be collected via procedures that guarantee preservation, retention and retrieval of information, and allow easy access for verification and audit. The patient's files, CRFs and other sources of primary data must be kept for future reference. Patient data must be handled in a way that maintains confidentiality, conforms to appropriate data protection legislation, and yet ensures accuracy. The condition of the patient before treatment, and the response to the treatment, including the observations of the assessor, the feelings of the patient and possible adverse effects, need to be fully documented.

All efforts should be made to maintain error-free records and to have as little missing data as possible.

Trial participants should receive adequate support to enable them to provide full data on their experience during the trial. Modern methods of data collection using the internet may help to ensure data is accurately recorded.

11. Trial Reporting

All CHM trials should conform to the guidelines laid down in the 22 item Herbal CONSORT Consolidated Standards of Reporting Trials) checklist (see appendix). A TCM specific adaptation of these CONSORT guidelines-the Elaborated Checklist of Reporting Randomized Controlled Trials of Chinese Herbal Medicine-may also be used and this is available from <http://www.consort-statement.org/extensions/interventions/>

This will ensure that trials are reported adequately and transparently and will prevent the poor reportage that has undermined much of CHM clinical research.

All CHM trials should be registered in either the EU or Chinese database of clinical trials. In order to avoid publication bias and to gain a true reflection of the impact of a medical intervention on a disease and any associated side effects it is important that all registered trials are written up according to the CONSORT checklist and are submitted for publication.

12. Implementation of Research

It is important for clinical researchers to make recommendations relating to how their conclusions (both positive and negative) can be implemented and disseminated both within the context of their own health structures and also worldwide.

This refers back to the earlier section 4.2 on identifying herbal stakeholders. For practitioners clinical trial data can be used to clarify issues relating to best practice. For patients the same data can be used to decide whether or not to opt for CHM treatment. For service providers clinical research can be used to decide whether to incorporate CHM within mainstream health care. Finally research data may be used to progress the development of new herbal drugs.

13. Methodological challenges to CHM research

There are several basic research techniques that must be urgently incorporated within CHM clinical trials. In particular these include:

- Adequate randomization and allocation concealment
- Blinding-when possible and appropriate
- The application of whole system research methodology to ensure that an accurate pragmatic assessment of the impact of CHM is made
- The use of literature reviews, peer reviews and alliances between researchers and practitioners to ensure model validity for CHM
- The use of internationally validated outcomes measures to record clinical changes and the development of validated TCM/ CHM specific measures to capture the kind of changes deemed important within Chinese medicine.

Recent years have seen a resurgence of interest from pharmaceutical companies looking to develop new drugs from CHM. While this may broaden the availability and affordability of CHM it is important that drug development is seen as just one possible end of the spectrum of CHM intervention. Traditionally the great strength of CHM has been regarded as the ability to write individualized prescriptions that are adapted according to changes in the clinical status of the patient. This is a different form of medicine from the dispensing of standardized herbal drugs. However these approaches can develop a mutually reinforcing rather than mutually exclusive relationship and it is hoped that this will be the case in the short and longer-term future.

14. The role of the “omic” technologies in CHM research

The development and application of the “omic”-technologies (in a commercial setting often implemented as high-throughput screening (HTS)) is in the process of significantly changing research perspectives towards traditional medicines including CHM. With “omics”, a multitude of molecules on the gene (genomics, transcriptomics), the protein (proteomics) or the metabolite level (metabolomic) including the dynamic metabolite response (metabonomic) can be estimated simultaneously, providing an innovative technological platform for an analysis of the composition of complex mixtures and their multi-targeted mode of actions.

These technical developments open the possibility that the search for single “active principles” in plants, based on the assumption that a plant has one or a few ingredients that determine its therapeutic effects, can now be extended into an approach that is more appropriate to traditional systems of medicine like CHM. In these systems it is generally assumed that the coaction of all ingredients of the plant(s), generally termed “synergy”, will bring about the maximum therapeutic efficacy. (For the definition of synergy from a pharmacological perspective please see Wagner & Ulrich-Merzenich et al. 2009a,b). The “omic” technologies provide a promising tool to cope with the analytic challenges arising from this approach in several different domains:

- authenticity and quality of plant material
- analysis of the mode of action of single plants and multi-component mixtures
- assessment of the toxicity of CHM
- Drug metabolism (individual drug responses)
- Integration of Chinese Medicine patterns into Western diagnostics

14.1 The authenticity and quality of the plant material:

Establishing authenticity and herb quality has historically relied on morphological and chemical methods. Metabolomic fingerprinting by GC-MS, HPLC-MS or NMR-spectroscopy

(for abbreviations see glossary) are now increasingly being used with the aim of developing metabolomic profiles. DNA-based assays have also been introduced to complement the morphological and chemical methods in order to generate molecular “bar codes” for the correct identification of medicinal plants (Sucher & Carles 2008). A recent review (Heuble 2010) of the most commonly used DNA-based technologies (RAPD, RFLP, ARMS, CAPS, AFLP, DAF, ISSR, SSR, sequencing, hybridization and microarrays; for abbreviations see glossary), includes comments on the strengths and the limitations of the different techniques using examples from Chinese medical plants .

To cope with the increasing amount of data generated by the use of the different techniques, there is an increasing demand to establish open access data banks in a multidisciplinary effort for medicinal plant research and to include e.g. the already available data (profiles) from the European Pharmacopeia, in order to develop a common standard for the characterisation of plants (Ulrich-Merzenich et al. 2010). This would be desirable as a long-term objective for CHM. In the meantime basic plant material used in clinical trials should be quality assured using conventional methods of standardisation (voucher specimens, chromatographic fingerprint, HPLC-fingerprints, quantification of known lead/surrogate substances and if possible the application of fixed contents of biological active substances).

The present EMEA guidelines on quality of combination herbal medicinal products/Traditional medicinal products (EMEA/CVMP/214869/2006) and the Guidelines for active substances (EMEA/CVMP/297/97) covering manufacturing issues like the qualification of impurities, stability and validation are recommended for further reading/orientation.

14.2 Analysis of the mode of action of single plants/ plant constituents and multicomponent mixtures:

At present, most of the data and thus evidence evaluating the mode of action of CHM relies on the analyses of water or alcoholic extracts prepared from single plants, rather than from traditional multi-herb decoctions. However relating a specific mode of action to single or even several plant components is highly problematic. Plant(s) have a multitude of

components, which differ in their composition with the method of preparation. Interaction between these compounds and with the target metabolism will also differ according to the composition as well as the preparation. The CHM-therapy is multi-targeted and is not adequately explained by an over simplistic focus on single targets.

The application of the “omic” technologies will support the evaluation of the multi-target mode of actions of plants that result from both the way they are prepared and combined within a herbal formula. Their use, however, cannot solve compositional changes of plant(s) or their preparations, but they will eventually support a fast identification of “surrogate” plant components which represent the activity of the plant extract which then could be used to provide markers for standardization of herbal products.

The primary focus of research at present should be the reproducibility of profiles of plant components, or their combinations, for the various mode of actions in various experimental models using different “omic” technologies. Issues like the permitted magnitude of variation for each technology still need to be addressed. The inclusion of available pre-clinical (and clinical) data using “omic”-techniques in the documentation of clinical trials would be desirable.

14.3 Assessment of the toxicity of CHM

Even though CHM is commonly regarded safe, incidents of nephrotoxicity from the use of *Aristolochia* species, reports of hepatotoxicity, and adulteration of herbal products with conventional drugs have created understandable public health concerns about CHM. In the meantime most EU member states have taken regulatory action to protect the public from unlicensed medicines containing toxic *Aristolochia* species (EMA/HMPC/138381/2005). However, as a consequence, increasing attention has been placed on toxicity studies. Melchart et al. (2001) for example demonstrated that about 3.5 % of the analysed CHM imported from China was contaminated with heavy metals.

The European Medicines agency (EMA) regulates the safety of marketed herbal medicinal products by several actions including producing guidelines on the safety of medicinal products in relation to teratogenicity, genotoxicity, carcinogenicity and toxicokinetic data

(see EMEA/HMPC/32116/2005). Recommendations in the form of public statements on different potentially toxic Chinese plants may be obtained via the EMEA/HMPC-homepage e.g. on *Cimicifugae racemosa* rhizome (EMEA/269259/2006). These information pages should be consulted before initiating clinical trials.

The introduction of the “omic”-technology into toxicology assessments may especially in the field of toxicogenomics, in a mid term perspective, offer tools to enable faster predictions of the toxicological potential of single and also importantly multi-component preparations. Toxicogenomics combines insights from toxicology, genetics, bioinformatics and other omic-technologies with the aim of predicting toxicity and potential adverse events on the basis of molecular expression profiles (Ulrich-Merzenich et al. 2009). Gene expression data are expected to be more sensitive than traditional toxicological endpoints (Searfoss et al.2004).

Recently the National Research Council of the US National Academy of Science, *Toxicity Testing in the 21st Century* has initiated a discussion on whether to base the assessments on “mechanisms and toxicant modes of actions” (Hartung and McBride 2011) and how to identify “pathways of toxicity” (Hartung and McBride 2011). Hartung and McBride (2011) proposed very recently the “Mapping of the human Toxome” as the basis for a new testing approach facilitating the identification of non-toxicity.

These are the consequences of the continuous increase of the use of “omic” technologies in clinical and experimental trials. In addition there is, as already mentioned in chapter B), also an ongoing collaborative effort to establish a public infrastructure on an international scale for a toxicogenomic database. An overview of the efforts in the public sector to create a toxicogenomic database has been given by Mattes et al. (2004). These databases are constantly updated and can already be used for the screening of potentially toxic ingredients of CHM, e.g. triptolides from *Tripterygium*-species. Theoretical information about the potentially toxic endpoints can now be obtained before starting a trial.

Recently it was shown that the combination of in vivo gene-expression profiles with the application of such theoretical screening tools appears to be useful for the prediction of potential adverse events (Ulrich-Merzenich et al. 2011). These analyses yielded also the result that

multiple ingredients in a herbal preparation may not necessarily increase the number of potentially adverse events. Nevertheless, these current analyses, even though based on *in vivo* data, are presently still only a theoretical exercise strongly depending on the data base used for such an analysis. In addition, these databases do not (yet) give information on concentration limits for toxic effects and many of the plant ingredients may not yet be found.

At the same time these databases are constantly developing with more and more array data being entered allowing an increasingly precise picture on molecule networks, their cross signalling and their final relevance for biological functions including adverse events (Ulrich-Merzenich et al. 2011). For current research into CHM using these tools would be desirable. However, in the long term, the toxicogenomic assessments along with other omic-methods (e.g. proteomics, metabolomics), in conjunction with traditional toxicology testing, should become part of the standard assessment for the quality and safety of CHM.

14.4 Drug metabolism (individual responses)

In addition to the potential toxicity of plant components or of their metabolites, the potentially different metabolisation capacity of each patient should also be considered. The metabolisation of drugs depends to a certain degree on the genotypes of key liver enzymes. For example there are 74 allelic variants for cytochrome P450 (CYP) and a series of subvariants for CYP2D6. Based on these genotypes patients have been classified into ultrarapid, extensive, intermediate or poor metabolizers – primary related to lipophile basic substances (Fleeman et al. 2010, de Leon et al. 2009). Thus, knowledge of different gene profiles of patients will enable predictions of possible toxic effects - not only from synthetic drugs, but also from CHM. These data may be instrumental in solving questions regarding major differences in the response to CHM. (The FDA of the USA has already named tests (e.g. the AmpliChip CYP450) as suitable for the use in clinical studies (de Leon et al. 2009)). These recommendations should support the safe use of presently available CHM, but also facilitate the development of novel, safe methods for the administration of CHM formulations.

14.5 Integration of Chinese Medicine (CM) patterns into Western diagnostics

Chinese medicine identifies and treats “Chinese medicine patterns” (Zhang et al. 2011) which cannot easily be correlated with Western diagnostics. At the same time the individualization in the CHM treatment is based on these CM patterns: “One formula based on one pattern”. Recent efforts have been undertaken to rationalize different CM disease patterns by omic-technology (Zhang et al. 2011, Jiang M 2011, Zheng et al 2011) and to develop profiles for the different disease patterns within one western diagnosis in order to predict responsiveness to Western or Chinese medicine. This research direction is likely to support the rationalization and even more important the integration of Chinese herbal medicine into Western medicine and mainstream healthcare.

15. References

- Allin KH, Nordestgaard BG, Zacho J, Tybjaerg-Hansen AT and Bojesen SE,. C-Reactive Protein and Risk of Cancer : A Mendelian Randomisation Study. *J. Nat.Cancer Institute*, 2010;102: 202-206
- Bauer R, Franz G. Modern European Monographs for Quality Control of Chinese Herbs. *Planta Med* 2010;76:2004-2011.
- Bellamy N, Buchanan WW. Clinical evaluation in rheumatic diseases: In McCarty DJ, Koopman WJ editors. *Arthritis and allied conditions*. 12th ed. Philadelphia: Lea&Febinger:1993:151-78.
- Bensky D, Gamble A (1986). *Chinese Herbal Materia Medica*. Seattle. Eastland Press.
- Bensoussan A, Talley N, Hing M, Menzies R, Guo A, Ngu M. The treatment of Irritable Bowel Syndrome with Chinese Herbal Medicine : A Randomized Controlled Trial’ , *The Journal of the American Medical Association*, 1998; 280:1585-1589.
- Bennett DA. An introduction to instrumental variables--part 2: Mendelian randomisation. *Neuroepidemiology*. 2010;35(4):307-10. Epub 2010 Oct 29.
- Campbell MJ & Machin (1999) *Medical Statistics: A Commonsense Approach*, Wiley.
- Chen L, Davey Smith G, Harbord RM, Lewis SJAlcohol intake and blood pressure: a systematic review implementing a Mendelian randomization approach. *PLoS Med*. 2008 Mar 4;5(3):e52.
- Chen RF, Lin QY, Xu YZ, et al., 2009. Clinical research on yiweisan granules for chronic gastritis.
- Chow SC & Chang M,. Adaptive design methods in clinical trials – a review. *Orphanet Journal of Rare Diseases*. 2008; 3: 1-13.
- Cirulli J, McMillian WD, Saba M, Stenehjem D Adaptive trial design: its growing role in clinical research and implications for pharmacists. *Am J Health Syst Pharm*. 2011;68(9):807-13.
- Colquhoun 2009. DC’s Improbable Science, <http://www.dcsience.net>
- Cragg, G.M., Boyd, M., 1996. Drug discovery and development at the National Cancer Institute: the role of natural products of plant origin. In: Balick, M.J., Elisabetsky, E., Laird, S.A. (Eds.), *Medicinal Plan Resources of the Tropical Forest*. Columbia University Press, New York, pp. 101–136.

Craig P, Dieppe P, Macintyre S. Developing and evaluating complex interventions: the new Medical Research Council guidance BMJ 2008; 337:a1655.

Crow R, Gage H, Hampson S, Hart J, Kimber A, and Thomas H, "The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review," Health Technology Assessment, 1999;3:1–96,.

Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M; Medical Research Council. Guidance Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337 a1655.

Creswell JW (2003): Research design: qualitative, quantitative, and mixed methods approaches. Thousand Oaks : Sage London

Davey Smith G. Capitalizing on Mendelian randomization to assess the effects of treatments. J R Soc Med. 2007;100(9):432-5.

Debelle FD, Vanherweghem JL, Nortier JL, Aristolochia acid nephropathy: a world wide problem: Kidney Int 2008, 74(2):158-69.

Devereaux PJ, Bhandari M, Clarke M, Montori VM, Cook DJ, Yusuf S, Sackett DL, Cinà CS, Walter SD, Haynes B, Schünemann HJ, Norman GR, Guyatt GH. Need for expertise based randomised controlled trials. BMJ. 2005;330(7482):88.)

Devilley G & Borkovec T. Psychometric properties of the credibility/ expectancy questionnaire Journal of Behavior Therapy and Experimental Psychiatry 2000; 31:73-86

Dobos G, Tan L, Cohen M, McIntyre M, Bauer R, Li X, Bensoussan A. Are national quality standards for traditional Chinese herbal medicine sufficient? Current governmental regulations for traditional Chinese herbal medicine in certain Western countries and China as the Eastern origin country. Complementary Therapies in Medicine. 2005;13(3):183-190.

EMA/ CVMP/214869/2006

EMA/ CVMP/297/97

EMA/ HMPC/138381/2005

EMA/ HMPC/32116/2005

EMA/269259/2006

Farquhar (1994). *Knowing Practice: The Clinical Encounter of Chinese Medicine*. Westview press, Boulder & Oxford.

Fleeman N, McLeod C, Bagust A, Beale S, Boland A, Dundar Y et al. The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation. *Health Technol Assess* 2010;14(3).

Flower A, Lewith G, Little P. Seeking an Oracle: Using the Delphi Process to Develop Practice Guidelines for the Treatment of Endometriosis with Chinese Herbal Medicine. *The Journal of Alternative and Complementary Medicine*. 2007;13(9): 969-976.

Flower A, Liu JP, Chen S, Lewith G, Little P. Chinese herbal medicine for endometriosis. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD00656

Flower A., Lewith G., Little P., Combining rigour with relevance: A novel methodology for testing Chinese herbal medicine. *J. Ethnopharmacology* 2011;134:373 – 378.

Gail MH & You WC A Factorial Trial Including Garlic Supplements Assesses Effect in Reducing Precancerous Gastric Lesions. *J. Nutr*. 2006; 136:813S-815S.

Goldbach-Mansky R, Wilson M, Fleischmann R, et al. Comparison of Tripterygium wilfordii Hook F Versus Sulfasalazine in the Treatment of Rheumatoid Arthritis: A Randomized Trial. *Annals of Internal Medicine* 2009; 151: 229-240.

Grant SJ, Bensoussan A, Chang D, Kiat H, Klupp NL, Liu JP, Li X. Chinese herbal medicines for people with impaired glucose tolerance or impaired fasting blood glucose. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD006690

Green J, Thorogood N. *Qualitative Methods for Health Research*. Sage Publication. London. Thousand Oaks. New Delhi. 2004: 175-186

Gerd Herold u. Mitarbeiter: Herold: *Innere Medizin*, Köln 2009

Hartung T, McBride M. Food for Thought. on Mapping the Human Toxome. *Altex*2011; 28: 83-93.

Heuble G. New aspects of DNA-based authentication of Chinese medical plants by molecular biological techniques. *Planta medica* 2010; 76:1963-1974.

Hlubocky FJ, Ratain MJ, Wen M, Daugherty CK. Complementary and alternative medicine among advanced cancer patients enrolled on phase I trials: a study of prognosis, quality of life and preferences for decision making. *J Clin Oncol* 2007;25:548-554.

Huang JK, Franklin RJ (2011) Regenerative medicine in multiple sclerosis: Identifying pharmacological targets of adult neural stem cell differentiation. *Neurochem Int*.

IpsosMORI (2009). Public perceptions of Herbal Medicine.
<http://www.ipsos-mori.com/researchpublications/researcharchive/poll.aspx?oItemId=2307>

Jiang M, Xia C, Chen G, Lu C, Zha Q, Yan X, Correlation between cold and hot pattern in traditional Chinese medicine and gene expression profiles in rheumatoid arthritis. *Front Med* 2011;5(2):219-28.

Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically Elevated Lipoprotein (a) and Increased Risk of Myocardial Infarction. *JAMA* 2009; 301 (22) 2331-2339.

Kaphle K, Wu LS, Yang NYJ and Lin JH. Herbal Medicine Research in Taiwan. *Evidence-based Compl. and Alt. Medicine*. 2006 ;3(1) :149-155.

de Leon J, Susce MT, Johnson M, Hardin M, Lorraine M, Shao A et al. DNA Microarray Technology in the clinical environment: the AmpliChip CYP450 Test for CYP2D6 and CYP2C19 Genotyping. *CNS Spectr* 2009;14(1):19-34.

Leung PC, Fong H, Xue CC (2006). Current Review of Chinese Medicine-quality control of herbs and Herbal material. *Annals of Traditional Chinese Medicine Vol 2*. World Scientific Press.

Lewith G, Jonas B, Walach H. Balanced research strategies for complementary and alternative medicine p12-14. In *Clinical Research in Complementary Therapies* ed Lewith G, Jonas B, Walach H. 2002. Churchill Livingstone.

Lewith G, Brien S, Barlow F, Eyles C, Flower A, Hall S, Hill C, Hopwood V: The Context and Meaning of Placebos for Complementary Medicine. *Forsch Komplementmed* 2009;16:404–412

Lewith G, Brien S, Barlow F, Eyles C, Flower A, Hall S, Hill C, Hopwood V: The meaning of evidence: Can practitioners be researchers? *Forsch Komplementmed* 2009;16:343–347

Linde K, Witt C.M., A. Streng et al., “The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain,” *Pain*, 2007;128: 264–271)

Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat.
<http://www.ncbi.nlm.nih.gov/pubmed/9116551> *BMJ*. 1997;314(7082):722-7

Liu JP. Qualitative research methodology in evidence-based Chinese medicine. *People's Medical Publishing House*. 2009:201-229

Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR; ukCAP Trial Group

Aspirin and folic acid for the prevention of recurrent colorectal adenomas. *Gastroenterology*. 2008 Jan;134(1):29-38. Epub 2007 Oct 10.

Ma YP, Liu XQ, Chen FK,. Comparison of Xiexintang dispensing granules and standard decoction with 3D-HPLC fingerprint chromatogram. *Chin Trad Pat Med* 2006; 28, 317-321.

Manheimer E, Wieland S, Kimbrough, Ker Cheng K and Berman BM. Evidence from the Cochrane Collaboration for Traditional Chinese Medicine Therapies. *The Journal of Alternatice and Complementary Medicine*. 2009;9:1001–1014.

Marks D, Yardley L, 2004. *Research Methods for Clinical and Health Psychology*. First ed. Sage, London.

Mattes WB, Petti SD, Sansone SA, Busel PR, Waters MD. Database development in toxicogenomics: Issues and Efforts. *Environ Health Perspect*. 2004;112(4):495.

Melchert D, Wagner H, Hager S, Selber R, Ernst E. Quality assurance and evaluation of Chinese medical drugs in a hospital of traditional Chinese medicine. *Alt Ther Health Med* 2001; 7:S24

Melchart D, Weidenhammer W, Linde K, Saller R. Quality profiling for complementary medicine: the example of a hospital for traditional Chinese medicine. *J Altern Complement Med* 2003, 9(2): 193-206.

MOH 2008: <http://www.moh.gov.cn>

Mondloch M.V, Cole D.C., and Frank JW, “Does how you do depend on how you think you’ll do? A systematic review of the evidence for a relation between patients’ recovery expectations and health outcomes,” *Canadian Medical Association Journal*, 2001;165:174–179.

Muller HH and Schafer H, Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and classical group sequential approaches, *Biometrics* 2001; 57: 886-891.

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

Pocock SJ 1979. Allocation of Patients to Treatment. *Clinical Trials Biometrics*, 1979;3:183-197

SATCM 2008: <http://www.satcm.gov.cn>

Sheehan, M P, Atherton D J. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative eczema’, *British Journal of Dermatology*, 1992; 126; 179-184.

Scheid V. (2002) *Chinese Medicine in Contemporary China: Plurality and Synthesis*. Duke University Press, Durham & London

Scheid V. (2007) *Currents of Tradition in Chinese Medicine 1626-2006*. Eastland press, Seattle.

Schipper H, Clinch J, Powell V: Definitions and conceptual issues: In *Quality of Life Assessments in Clinical Trials*. Edited by Spilker. New York, Raven Press. 1990;11-24.

Schulz KF & Grimes DA a. Blinding in randomised trials: hiding who got what. *Lancet*. 2002;359(9307):696-700.

Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet*. 2002;359(9306):614-8.

Searfoss GH, Tomothy P, Jolly R, Jolly RA. The role of transcriptome analysis in pre-clinical toxicology. *Curr Mol Med* 2004; 5:53.

Smith GD & Ebrahim S, 2003. Mendelian randomisation : can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J of Epidemiology*. 32 1-22.

Sucher, NJ, Carles, MC. Genome-based approaches to the authentication of medicinal plant. *Planta Med*. 2008; 74 (6): 603–623.

Tang JL, Zhan SY, Ernst E. Review of randomised controlled trials of traditional Chinese medicine. *BMJ*, 1999; 319:160-161.

THMPD: Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

Ulrich-Merzenich G, Zeitler H, Panek D, Vetter H, Wagner H. Application of the „Omic“-technologies in phytomedicine, *Phytomedicine* 2007;14 (1):70-82.

Ulrich-Merzenich G, Panek D, Zeitler H, Wagner H, Vetter H. New perspectives for synergy research with the „Omic“-technologies. *Phytomedicine*, 2009;16(1):495- 508.

Unschuld P (1998). *Chinese Medicine*. Paradigm Publications, Brookline, Massachusetts.

Van Wietmarschen, H., Yuan, K., Lu, C., Gao, P., Wang, J, Xiao, C., Yan, X., Wang, M, Schro. Systems biology guided by Chinese medicine reveals new markers for sub-typing rheumatoid arthritis patients. *Journal of Clinical Rheumatology* 2009;15:330-337

Wagner H, Ulrich-Merzenich G. Synergy research: Approaching a new generation of phytopharmaceuticals. Part I, *Phytomedicine*, 2009; 16(2-3), 97- 110.

Wagner H, Bauer R, Melchart D, Xiao PG, Staudinger A (Editors): *Thin-Layer and High Performance Liquid chromatography of Chinese drugs Vol 1*, Springer Wien New York 2011 2nd Edition.

Wang G, Mao B, Xiong ZY, Fan T, Chen XD, Wang L, Liu GJ, Liu J, Guo J, Chang J, Wu TX, Li TQ (2007); CONSORT Group for Traditional Chinese Medicine. The quality of reporting of randomized controlled trials of traditional Chinese medicine: a survey of 13 randomly selected journals from mainland China. *Clin Ther*.2007; 29(7):1456-67.

Wang J, Chen H, Hao Y, Zhang Y 2001 Alcohol ingestion and colorectal neoplasia: a meta-analysis based on a Mendelian randomization approach.. *Colorectal Dis* 2011;13(5) :71-78.

Wang L, Zhou GB, Liu P, Song JH, Liang Y, Yan XJ, Xu F, Wang BS, Mao JH, Shen ZX, Chen SJ, Chen Z Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia.. *Proc Natl Acad Sci U S A*. 2008;105(12):4826-31.

White P, Lewith G, Prescott P, Conway J. Acupuncture versus Placebo for the Treatment of Chronic Mechanical Neck Pain: A Randomized, Controlled Trial *Ann Intern Med*, 2004 141:911-919

Wu TX, Qi Z, Liu JX, Yang X, Moher D (2008). Assessing the quality of Cochrane systematic reviews of Traditional Chinese Medicine. Oral presentation at the Cochrane colloquium, Sao Paulo, Brazil.

Xu W, Towers AD, Li P, Collet JP. Traditional Chinese medicine in cancer care: perspectives and experiences of patients and professionals in China. *Eur J Cancer Care (Engl)*. 2006;15(4):397-403.

Yan B, Hao H et al. Metabonomic phenotype and identification of «heart blood stasis obstruction pattern» and “qi and yin deficiency pattern” of myocardial ischemia rat models. *Sci China C Life Sci* 2009, 51(1):1081-90.

Yu H, Liu JP. Qualitative Method and Its Application Status in Healthcare. *The Journal of Evidence-Based Medicine*, 2008,8(5):292-296,300. [Chinese]

Yu H, Liu JP, Wang SC. A qualitative study method used for deep describing TCM physician-patient communication process. *Journal of Beijing University of Traditional Chinese Medicine*,2010;33(11):732-736

Zheng G, Jiang M, He M, H X, Zhao J, Guo H. Discrete derivative: a data sclicing algorithm for exploration of sharing biological networks between rheumatoid arthritis and coronary heart disease. *Biodata mining* 2011,4.18.

Zick SM, Schwable H, Flower A, Chakraborty B, Hirschhorn K. Unique Aspects of Herbal Whole System Research. *Explore (NY)*. 2009;5(2):97-103.

16. Glossary

Cross sectional survey-the collection of data at a single point of time from a sample population. This differs from a **longitudinal survey**-when responses from the sample population are evaluated over a period of time.

Decoction (汤 Tang)-is the most common traditional method of dispensing Chinese herbal medicine. Commonly used for dried plant material in the form of bark, root or wood. Plant material is kept in cold water and then slowly heated to cook for 10 to 15 minutes. Thereafter its passed through a sieve.

‘Efficacy’ refers to ‘the extent to which a specific intervention is beneficial under ideal conditions’. It concentrates primarily on the causal effects of a treatment e.g. by comparing an intervention to a placebo.

‘Explanatory trial’ is a randomized controlled trial designed with the purpose of measuring ‘efficacy’ under experimental (ideal) conditions. For example, inclusion and exclusion criteria are usually used to select patients without any co-morbidity and who are expected to have excellent compliance.

‘Effectiveness’ is a ‘measure of the extent to which an intervention when deployed in the field in routine circumstances does what it is intended to do for a specific population’. In other words ‘effectiveness’ reflects whether a treatment is beneficial under conditions close to routine care and effectiveness studies use a more ‘pragmatic’ approach.

Equipoise- a genuine uncertainty and lack of preference for one treatment over another treatment within the medical community and in patients. This is a pre-requisite to ethical experimentation on human subjects using the RCT research design.

Investigators Brochure-a compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

‘Pragmatic or practical clinical trial’ is a randomized controlled trial designed with the purpose of informing decisions about routine practice. Pragmatic trials are designed to find out about how effective a treatment actually is in everyday practice and this design is of relevance for complementary medicine. The extension of the CONSORT statement is intended to improve the reporting of such trials and focuses on applicability.

Observational study-a study that investigates the effectiveness of a treatment without using randomisation to control for bias

Qualitative research-explores the concrete experiences of individuals in their particular contexts as expressed through the written and spoken word or through non-verbal means of communication. It does not provide numerical data that can be statistically analysed (quantitative research) but it can provide an in-depth understanding of the complex experience of individuals, the groups they belong to and their understandings and experiences of an intervention like CHM which is often provided as a whole system of medicine.

TCM-Traditional Chinese Medicine: an attempt by the Communist Chinese government that started in the 1950’s and early 1960’s to combine and systematise various strands of Chinese medicine into a logical, coherent whole that was clear, consistent and materialistic. Whilst it has enabled the standardised teaching and practice of Chinese medicine that has led to a resurgence of CM both within and outside China it has been criticised for being an over-simplistic and reductive representation of CM.

17. Abbreviations:

AFLP: Amplified fragment length polymorphism

ARMS: Amplification refractory mutation system

CAPS: Cleaved amplified polymorphic region

CHM: Chinese herbal medicine

DAF: DNA amplification fingerprinting

GC: Gas-chromatography

HPLC: High performance liquid chromatography

HTS: High throughput screening technology

ISSR: Inter simple sequence repeat

MS: Mass-spectrometry

RAPD: random amplified polymorphic DNA

RFLP : Restriction fragment length polymorphism

SSR: simple sequence repeats

18. Recommended further reading

Flower A., Lewith G., Little P., Combining rigour with relevance: A novel methodology for testing Chinese herbal medicine. *J. Ethnopharmacology* 2011;134:373 – 378.

Scheid V & MacPherson H (2012). *Integrating East Asian medicine into contemporary healthcare*. Churchill Livingstone.

Lewith G, Jonas W, Walach H (2011). *Clinical Research in Complementary Therapies*, 2nd Edition. Churchill Livingstone.

Witt CM, Linde K. *Clinical Research in Complementary and Integrative Medicine. A Practical Training Book*. ISBN: 978-0-7020-3476-3, Elsevier GmbH München 2011;189pg

Yu H, Liu JP. A qualitative study of exploring the therapeutic components of traditional Chinese medicine as a complex intervention through grounded theory. *Journal of Chinese integrative medicine*. 2010;8(10):928-943

Ulrich-Merzenich G, Zeitler H, Panek D, Vetter H, Wagner H. Application of the „Omic“-technologies in phytomedicine, *Phytomedicine* 2007;14 (1):70-82.

Ulrich-Merzenich G, Panek D, Zeitler H, Wagner H, Vetter H. New perspectives for synergy research with the „Omic“-technologies. *Phytomedicine*, 2009;16(1):495- 508.

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