



Guidelines for randomised controlled trials investigating Chinese herbal medicine

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ABSTRACT

Ethnographic relevance: Clinical trials investigating Chinese herbal medicine (CHM) have been frequently criticised for their lack of scientific rigour. As part of the GP-TCM project a team of experienced clinical researchers and CHM practitioners have developed clinical trial guidelines for CHM that combine an appreciation for traditional methods of practice with detailed and practical advice on research methodology.

Materials and methods: This paper presents an executive summary of this work. It introduces the practice of CHM and the key considerations that need to be addressed whilst researching this traditional medical system.

Results: These guidelines emphasise the importance of identifying best practice, and then developing and applying appropriate and rigorous research methodologies to investigate CHM as a whole system.

Conclusions: It is hoped that this will encourage a thoughtful and meticulous process of investigation that will clarify the contribution that CHM can make to our future healthcare. Innovative new approaches are considered including the application of the new “omic” technologies and systems biology as a way of enhancing our understanding of traditional practice

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1. Background

Our primary aim in developing these guidelines was to improve and develop randomised controlled trial (RCT) methodologies to investigate the clinical practice of Chinese herbal medicine (CHM). The quality of clinical research in this area has been perceived as a major issue for many years by researchers, clinicians and regulator authorities' internationally. The GP-TCM consortium (GP-TCM) has provided the ideal environment to develop this process initially for the European Union. The guidelines were developed by a team of experienced researchers from the EU and China as part of the GP-TCM project over a period from October 2010 to July 2011 and are available via the [GP-TCM website](http://www.gp-tcm.com) (GP-TCM). Particular attention has been paid to address the dilemma of maintaining the integrity of the practice of Chinese medicine (CM) and the complex, whole systems nature of CHM interventions, whilst subjecting CHM to robust research methodologies to investigate its safety and effectiveness. Various stages in the research process are described and

discussed and practical information on the design and implementation of a protocol is provided. Finally the new “omic” technologies are introduced as a means of employing the latest approaches in systems biology to model and deepen our understanding of the therapeutic pathways that may be involved in CHM.

This is intended as a practical document that can be used freely by CHM researchers from the initial stages of conception, through trial design and development, to the final process of reporting results. It is a consensus document that will inevitably evolve over time and through debate, evidence, and will be useful to national and international drug regulatory authorities.

2. Special considerations for CHM research

CHM is one component of CM that incorporates other treatment modalities such as acupuncture, moxibustion, tuina and qi gong (Maciocia, 1989). It has its own distinctive understanding of the causation and pathological process of disease, systematic methods of diagnosing and categorising illness, and a sophisticated approach to treatment of disease and health maintenance. CHM has a recorded history of over 2000 years (Unschuld, 1998). During its long history it has developed into many diverse forms of

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practice that are now common in East Asian countries, and appear to be making an increasing impact on healthcare systems throughout the world (Scheid, 2002). This has perhaps been accelerated by the development and marketing of effective pharmaceutical agents from herbs such as Artemisinin from *Artemisiae annuae* L. Despite its diversity and the depth of pharmacological evidence for the specific efficacy of herbs we believe there are several key components that unite the practice of CHM and that need to be considered when developing a CHM research programme.

Best practice of CHM is usually considered to involve providing an individualised treatment that may change over time in response to the health status of the recipient. Until recently the commonest route to deliver CHM was via water based herbal soups or decoctions (Bensky and Gamble, 1986). Since the 1960s new methods of delivering CHM have emerged including the use of concentrated powders, extracts, and injections. These guidelines discuss the various merits and shortcomings of the available delivery options, and propose a staged investigation of CHM, from traditional methods of practice to the more standardised, processed, and refined approaches that suit a modern pharmacological investigation. This should create an appropriate and scientifically rigorous pathway for the development of an effective, licensed, and widely available CHM products. We have chosen this strategic route in recognition of the knowledge embedded within CM over centuries of clinical practice but are by no means wedded to the belief that long term traditional use of a specific herb or herbal mixture can be taken as evidence of effectiveness or safety.

3. Key recommendations

1. Research ideas should emerge from positive experience in clinical practice and address current “effectiveness gaps” in conventional medicine, where treatment is either ineffective or associated with unacceptable adverse effects (Shan and Chi Ho, 2011). The design of the research should be tailored to provide the kind of information required by the main research stakeholders which is likely to include pragmatic and cost effectiveness studies.

It is essential that the research methodology that is selected is appropriate to answer the specific research question (see Table 1). These guidelines discuss how, for example, to investigate the specific efficacy of CHM, in the context of rigorously designed double blinded, explanatory trials, with a relatively homogenous population using a single intervention versus a control intervention. However, if we are considering the investigation of the ‘real world’ effectiveness of CHM, then pragmatic

Table 1
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 trial
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

trials with a heterogeneous population receiving more naturalistic treatment (that may include modalities such as acupuncture or tuina) should be used (see Fig. 1). Different research methods including N-of-1 trials, cross over studies, and factorial designs are introduced in the guidelines to encourage flexibility and sophistication in trial design. An N-of-1 trial may involve an individual being randomly assigned to Treatment A for a period of time before being switching to either an active or a placebo Treatment B, is a more controlled version of the case study that has informed CHM practice for hundreds of years.

The guidelines also discuss the value of qualitative research as a means of providing a deeper, more patient centred account of receiving CHM treatment. These approaches can be incorporated into quantitative mixed method designs to explore the complex nature of CHM intervention (see Table 3).

2. The development of a CHM research project should follow the UK Medical Research Council (MRC) guidelines for investigating a complex intervention (Craig et al., 2008). These guidelines describe mutually informing phases of research, rather than a simple linear progression. They recommend paying careful attention to model validity/best practice in the initial Developmental phases of research. These are then tested and refined in a Feasibility stage, before a more rigorous assessment in an Evaluation phase that will use models involving adequately powered and properly managed randomised clinical trials. Finally an Implementation phase assesses the ‘real world’ and long-term

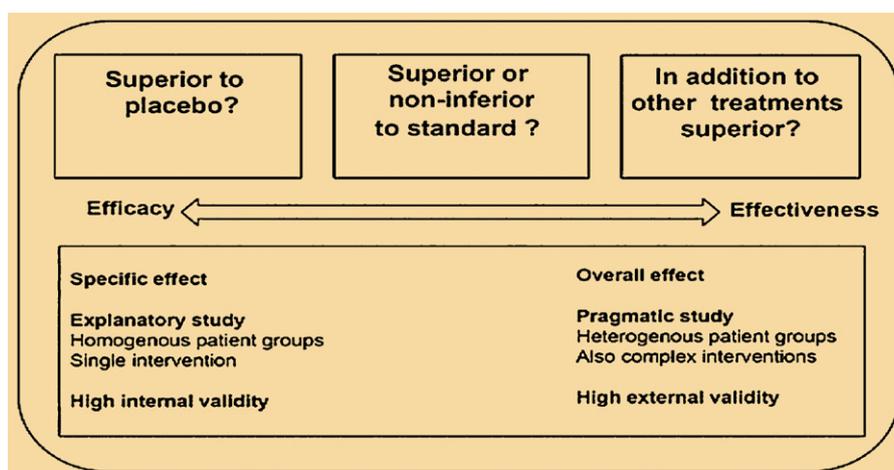


Fig. 1. The relationship between the research question and the corresponding study design (Witt, 2009).

Table 2
Pattern diagnosis and treatment in traditional Chinese medicine.

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

contribution that CHM makes to health care, and identifies areas for future research. During these research phases it will be necessary to adopt different research methods to address the different research questions being addressed (see Table 1).

Defining best practice is a complex process that includes the CHM notions of causation, patho-physiology, and disease treatment. We consider it is essential that CHM is investigated using a pragmatic and experiential based approach to create the best possible intervention, based on the information available, for the proposed study and study participants. An example of how various symptoms are grouped into patterns or syndromes, which then inform a choice of classical herbal formula that may then be individualised for a particular patient is given in Table 2. This approach is apparent in a recently published CHM paper describing a two-stage trial protocol. In the initial open phase a CM syndrome pattern that appears more responsive to a particular CHM intervention is identified. This is then followed by a second phase, double-blinded RCT, which only enrolls participants presenting with this syndrome (Zhang et al., 2011).

- We may eventually have a much greater understanding of the science involved which should then allow us to move away from this experiential approach but until we do so, it is essential that we recognise, evaluate, and work with this accumulated clinical experience. Defining best practice should involve reflective practice, a literature review (to include available research, contemporary text books and, where possible, classical CHM texts), and some form of peer review that provides a professional consensus to support the CHM treatment used within any clinical trial.
- In the design of treatment protocols using CHM herbal treatment may be:
 - Individualised*: where each participant is given an individualised prescription that may change over time. This is generally considered as the optimum way to deliver safe and effective CHM in most parts of the world.
 - Semi-standardised*: using CHM patterns or syndromes of disease to inform treatment or inclusion into a clinical trial to provide broadly targeted treatment.
 - Standardised*: this involves a single remedy being used for all participants in a trial. It has the advantage of making the

findings of the trial more generalisable but it does not conform to the generally held notions of best CHM practice.

We recommend that research progresses through these stages. Whilst it may not be practical to run an individualised trial, it is relatively straightforward to conduct clinical audits on individualised cases. These can then be used to help define best practice and may lead to the identification of 2 or 3 commonly occurring key syndromes and a narrow range of herbs that could be used in a semi-standardised research design. A generic treatment can also be developed to include benefits for the range of identified syndromes if appropriate.

5. Methods of CHM administration:

The delivery of CHM usually involves herbal formulae that may range in the number of ingredients from a single herb to complex formulae of over 20 ingredients. Typically though a CHM formula includes between 8 and 15 herbs that are divided into those with the primary therapeutic action (the 'Emperor' herbs); those that support this action and address other co-existing patterns (the 'Minister' herbs); those that reinforce the primary therapeutic agents and act to reduce adverse events (the 'Assistant' herbs); and finally the 'Envoy' herbs that focus the formula on a particular part or system of the body. There are several methods that can be used to administer CHM. Traditional use generally favours protracted boiling of the herbs to make decoctions, although alcoholic extracts and herbal pills are also commonly mentioned in the classical records. In recent years concentrated powdered extracts have become an increasingly common method of dispensing CHM. The use of these powders is potentially a great boom for producers, regulators and patients from the perspective of manufacture, quality control, reproducibility of product, patient adherence to the recommended treatment and subsequent marketing.

Best practice in China has been considered to involve the use of herbal decoctions (Bensky and Gamble, 1986) in order to preserve the range of the traditional synergies that may underpin the therapeutic effects of CHM. Taiwan and other Asian countries (Japan and Korea) are now increasingly using concentrated herbal powders as the basis for their prescriptions. Whilst this allows the production of a convenient, quality assured product there is some chromatographic evidence to suggest that

Table 3
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	Framework analysis; thematic analysis; grounded theory (Green and Thorogood, 2004)
What is involved within the whole consultation between CHM practitioners and patients? And how does it happen? (Yu et al., 2010)	participant observation; non-participant observation; interview (Yu and Liu, 2008)	Conversation analysis; thematic analysis (Liu, 2009)

the manufacturing process for concentrated powders leads to a reduction in known active compounds (Chen et al., 2009; Ma et al., 2006). However, a recent systematic review reported in the current issue of this journal, provides very preliminary evidence that calls the clinical implications of this assumption into question (ref) and suggests that concentrated powders may be as clinically effective as herbal decoctions. At present there is no definitive answer to this question. For the purposes of these guidelines the recommendations are:

- to include herbal decoctions at some stage of the CHM research process. This may be as part of a clinical audit, prospective observational study, or case series but it has been shown that rigorous double-blinded RCTs are possible with individualised CHM decoctions (Flower et al., 2011; Lechner et al., 2011);
- if it is not possible, for financial or pragmatic reasons, to use decoctions in a trial setting, then we recommend using concentrated powders derived from herbal decoctions, rather than simply aggregating the individual herbal powders. We consider that this will incorporate the traditional compositions of ingredients (formed during the preparation of the decoctions) that are probably important to the effectiveness and safety of CHM;
- if this is not possible, and only aggregated individual herb powders should be used, then this should be clearly recorded in the report of the trial methodology.

6. Blinding and randomisation

Although there are more than 17,000 RCTs currently published within the Chinese database (Tang et al., 1999; Wang et al., 2007), it has been estimated that less than 5% of these conform to internationally acceptable research standards (Wu et al., 2008) with respect to blinding and randomisation. The main causes for this are misconceptions about the meaning of these terms and the practical requirements for adequate blinding and randomisation. These guidelines, which will be available to Chinese researchers, describe several methods of randomisation that are appropriate to a variety of different clinical and research contexts and discuss issues relating to the importance of blinding in CHM clinical trials. It is hoped that they will lead to an increase in the standard and rigour of Chinese and European clinical trials that will prevent wasteful research and facilitate a more rigorous investigation of CHM.

7. Conducting a clinical trial:

The guidelines introduce the key components required to conduct a clinical trial. These include the complex ethical and legal considerations in the EU and in China that need to be taken into account before a trial can commence, such as the importance of a clear and consensus based study protocol, registering a trial on an international database, gaining ethical approval for the trial protocol, and using herbal products that meet the required standards for Good Manufacturing and Good Agricultural practice (GMP and GAP). Information is provided on how to access the various government agencies responsible for regulating these aspects of clinical trials.

There are also detailed sections in the guidelines on how to develop a trial protocol, discussion of the kinds of outcomes measures that should be used (including areas such as health economic analysis that are routinely neglected in CHM trials), the importance of long term follow up to detect sustained improvements in health and changes in rates of disease reoccurrence, and recommendations on how results should be reported, disseminated and implemented in accordance with the latest herbal CONSORT requirements. Particular emphasis is made to using accurate botanical nomenclature, and providing detailed accounts of how herbs are prepared and administered. The guidelines also propose the biochemical profiling of herbal

medicines used in a trial to safeguard the comparability of different studies, and to enable research that may be controversial to be reproduced.

8. The role of “omic” technologies and systems biology approaches in CHM research:

The development and application of the “omic” technologies is in the process of significantly changing research perspectives towards traditional medicines including CHM (Ulrich-Merzenich et al., 2007). With the “omic”-technologies, a multitude of molecules on the genetic level (genomics, transcriptomics), the protein level (proteomics), or at the level of metabolites (metabolomics), 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. At the same time system biology approaches aimed at obtaining, integrating and analysing complex data sets from different sources using interdisciplinary tools will provide a better understanding of causes and effects in biological networks (Van Wietmarschen et al., 2009).

These developments mean 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 evolve into an approach that is more appropriate to traditional systems of medicine like CHM and conceptually link the approaches used in TCM with systems biology and the emerging technology of individualising medicines in accordance with a person’s biological variability. In these systems it is generally assumed that overadditive or synergistic effects of all ingredients of the plant(s) will bring about the maximum therapeutic efficacy. The “omic”-technologies provide a promising tool to cope with the analytic challenges arising from this approach and the guidelines discuss their potential contribution 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.

4. Conclusion

These guidelines introduce the practice of CHM and describe key considerations that need to be addressed in the development of rigorous research methods for this traditional medical system. They emphasise the importance of identifying best practice, and then developing appropriate research methodologies to subject CHM to scientific scrutiny. It is hoped that these guidelines encourage a thoughtful and systematic process of investigation that will clarify the contribution that CHM can make to our future healthcare.

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