Ministry of Health Malaysia

NATIONAL COMMITTEE FOR RESEARCH AND DEVELOPMENT IN HERBAL MEDICINE (NRDHM)

GUIDELINES FOR THE CLINICAL EVALUATION OF T/CM INTERVENTIONS

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Message by

The Honourable Dato Chua Jui Meng,
Minister of Health of Malaysia

Traditional medicine has formed the basis of health care throughout the world since the earliest days of mankind and is still widely used. It has been estimated that nearly 80% of the world's population use some form of traditional and complementary medicine (T/CM). The use of herbal medicines is growing steadily worldwide, increasing at a rate of 10-20% annually.

Of the approximately 250,000 known plant species in the world today, it is estimated that only about 5% have been examined for their medicinal properties and 25% of all prescription drugs are based on plants belonging to only 40 species. There are at least 150,000 species of flowering plants in the tropics and in South East Asia alone, there are 35,000 species of which 8,000 are found in Malaysia. In the tropics, a total of 6,000 floral species have been reported to possess medicinal values. Of these, a total of 1,230 local species have been recorded as plants used in traditional medicines. Malaysia is one of the 12 mega biodiversity countries in the world and is nestled in the oldest rainforest in the world. It is also a melting pot of 3 important T/CM systems, namely the Malays, Chinese and the Indian traditional medicine systems and It is hardly surprising therefore to note the growing interest of T/CM amongst policy makers, researchers, clinicians, entrepreneurs and the community at large in this country.

This growing popularity and appeal of T/CM the world over, have created both an opportunity and the obligation for the Government to conduct proper scientific studies and evaluation in T/CM. It has been reported that an estimated USD 500 million is spent annually on T/CM compared to USD 300 million on modern medicine in Malaysia. There is now greater demand for evidence on the safety, efficacy and quality of T/CM products and practices.

I would like to therefore congratulate the **National Committee for Research & Development in Herbal Medicine (NRDHM),** the brainchild of the Ministry of Health, for producing several guidelines pertaining to herbal medicine research to ensure that good research practices, as well as authenticity, safety, efficacy of therapies involving herbal medicinal products are assured. These guidelines are indeed very timely and will serve to enhance consumer confidence in T/CM.

Dato Chua Jui Meng,
Minister of Health of Malaysia

Message by

Y Bhg Tan Sri Datu Dr. Mohamad Taha bin Arif
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The Ministry of Health (MOH) is responsible for ensuring the availability of appropriate, safe, effective health care services in the country. While much of the healthcare currently provided by the MOH is driven by modern medicine which is based on scientific evidence, there is a growing interest in the use of traditional and complementary medicine (T/CM) as either an alternative or an adjunct to modern medicine. The MOH launched the policy on T/CM in 2001 in recognition and anticipation of the increasing popularity of T/CM not only in this country but also worldwide.

The WHO encourages the integration of safe and efficacious T/CM into mainstream healthcare system. Before considering the integration of T/CM into our mainstream health care system, the MOH has the responsibility of ensuring that only appropriate, safe and effective herbal medicines of consistent quality are developed and available to those in need. It is also our responsibility to ensure that the herbal medicinal products not only meet the required product quality standards (GMP), but have also in place, the necessary evidence to support its safe and appropriate use in specific disease states (evidence-based therapeutic use). The development of such medicinal products needs to be carried out in a coordinated, systematic and scientific manner, similar to that of pharmaceutical drug development.

It is therefore gratifying to note that the Ministry of Health, through the **National Committee for Research & Development in Herbal Medicine (NRDHM)**, has produced four guidelines for researchers in T/CM to use as guidance documents to strengthen research and development in herbal medicine and thus bring the practice of T/CM to a higher level of quality for greater acceptance by providers of modern medicine and the public. The stage will then be set for the integration of modern and T/CM into mainstream healthcare system.

Tan Sri Datu Dr. Mohamad Taha bin Arif
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Message by

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There are generically three groups of traditional/herbal preparations in Malaysia: the Malay traditional preparations, the Chinese preparations, and the Indian traditional preparations. Within each of these groups are different remedies that are being compounded and sold for the same disease indication. It is very clear that there is a great deal of variation and secrecy as to the composition of these "local" remedies. Absence of standardisation is a common feature. The lack of collaboration and co-operation within the group and between groups make it difficult to develop a truly Malaysian traditional/herbal formulary for treatment of the different illnesses found in this country.

Some of the reasons delaying the development of a national formulary specific for herbal products include the lack of co-ordination between the traditional herbalists and feeble attempts to systematically evaluate locally available flora to identify active ingredients that will be viable commercially, especially in the context of the emergence of new chemical entities.

In order to facilitate the future development of traditional/herbal medicines in this country, one has to understand the processes and activities that need to be in-place to ensure that commercially viable herbal products can be systemically developed and internationally marketed. Acknowledging that herbal medicines can contribute to the economy of the country, the development of such medicinal products need to be carried out with some urgency.

The timely approval by the Malaysian Cabinet of the establishment of the **National Committee for Research & Development in Herbal Medicine (NRDHM)** in April 2002 under the auspices of the Ministry of Health and chaired by the Deputy-Director General of Health (Research and Technical Support) has given herbal medicine research the much needed catalyst to steer it in the right direction and in accordance with international standards.

The terms of reference of NRDHM include the development and coordination of the strategic master plan for R&D in herbal medicine research, the production of relevant guidelines to ensure quality, safety and integrity of data in line with local regulations, creation of harmonization, understanding and collaboration between researchers, identification of training and infrastructure needs in herbal medicine R & D, the setting of targets and facilitation of new product discovery and development and addressing issues pertaining to Intellectual Property Rights management.

Members of NRDHM include senior representatives from the various ministries, universities and appropriate stakeholder agencies such as the Science University of Malaysia, Agriculture and Research Development Institute, Drug Control Authority, Ministry of Science ,Technology and Environment, Ministry of International Trade and Industry , Ministry of Education, Malaysian Industry Government Group for High Technology, Malaysian Herbal Cooperation and the Institute for Medical Research.

The guidelines that have been prepared by NRDHM pertain to clinical research, standardization, claims and intellectual property rights management. They will serve as guidance documents to ensure rigorous quality in herbal medicine research and safety of our herbal products. It is hoped that the quality of studies conducted will be of the highest standards and generating findings and products that are accepted not only in Malaysia, but also globally.

These guidelines have been prepared in consultation with various existing guidance documents from the Federal Drug Control Authority (FDA), USA the World Health Organisation (WHO), European Union and Therapuetics Good Administration (Australia)

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Terms of Reference

- To develop, coordinate and monitor the strategic master plan for Research & Development in Herbal Medicine Research.
- To produce relevant guidelines to ensure quality, safety and integrity of data in line with local and international regulations.
- To create harmonization, understanding and collaboration between researchers.
- To conduct dialogues and other related activities for promotion of Herbal Research & Development.
- To identify training and infrastructure needs in Herbal Medicine Research & Development.
- To set targets and facilitate new product discovery and development.
- To address issues pertaining to Intellectual Property Rights Management.

Guidelines for the Clinical Evaluation of T/CM Interventions

1. General considerations

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. The Declaration of Helsinki issued by the World Medical Association in 1964, is the fundamental international document in the field of ethics in biomedical research and has influenced the formulation of international, regional and national legislation and codes of conduct. The Declaration amended several times, most recently in 2000, is a comprehensive statement of the ethics of research involving human subjects. The International Conference on Harmonisation (ICH) provides a unified standard for the conduct of clinical trials (ICH topic E6). The standard guidance which incorporates the principles of the Declaration of Helsinki outlines that clinical studies should be carried out according to ICH/ WHO (World Health Organisation) Good Clinical Practice Guidelines (GCP). Currently, this standard is being used for the European Union, Japan, United States, Canada, The Nordic countries and WHO.

The Ministry of Health Malaysia has formulated and produced the "Malaysian Guidelines for GCP" in 1999 to ensure that clinical trials carried out in Malaysia adhere to the ICH guidelines and that the accuracy and credibility of data as well as the integrity and confidentiality of trial subjects are protected.

This guidance document is intended to promote rigorous quality in herbal medicine research and safety of our herbal products. It must be stated that even though evidential requirements will be different from those required for pharmaceutical, the quality of the studies must be of the highest standards in order to ensure that these products are accepted not only in Malaysia, but also globally.

In addition to evaluating the safety and efficacy of traditional medicine through clinical trials, specific objectives pertaining to assessment of traditional medicine through clinical research may include the following:

- To evaluate traditional medicine in its own theoretical framework (e.g. mechanistic studies);
- To evaluate traditional medicine in the theoretical framework of conventional medicine (e.g. mechanistic studies);
- To compare the efficacy of different systems of traditional medicine and/or conventional medicine; and
- To compare the efficacy of different traditional practices within a system of traditional medicine.

2. Literature review

The starting point in the design of a research protocol is a complete literature review, including the traditional use of the proposed practice and product and existing scientific research in the field. Where little or no literature exists, the oral tradition and the source of this tradition needs to be clearly stated.

A review of the literature should identify the current level of evidence of efficacy and safety for the proposed intervention. Evaluation of the literature should follow well-established and accepted guidelines. However, meta- analysis in traditional medicine may be difficult, mainly due to the lack of large clinical trials of good quality. In addition, the efficacy of a particular treatment may also vary according to the skill and experience of the practitioner. These issues must be considered and kept in mind.

3. Clinical Considerations

Phase 1 studies are designed to determine safety associated with increasing doses in normal volunteers, as a precursor to phase 11 and PHASE 111 trials. In addition, phase 1 studies investigate toxicity and drug levels in states in which drug levels might be altered for example, in renal and hepatic impairment. Mechanisms of action are also investigated in phase 1.

Phase 11 studies evaluate the efficacy of a range of doses in individuals with disease. Phase 11 studies typically start by evaluating the maximum tolerated dose determined in the phase 1 normal volunteer studies. If the maximum dose is effective, dose ranging downward would be investigated. If the phase 1 dose is ineffective, dose ranging upward generally is performed. Phase 11 dose ranging studies use a relatively small number of patients per dose group. Placebo and standard intervention control groups may be included, but there will not be sufficient participants to compare statistically the botanical dose groups to the standard intervention group.

Phase 111 studies are expanded trials of safety and efficacy. They are performed after preliminary evidence suggesting efficacy for the intervention has been obtained. Phase 111 studies are intended to gather additional information about the efficacy and safety needed to evaluate the overall benefit-risk ratio of the intervention and to provide an adequate basis for general clinical use . Phase 111 studies usually include large numbers of participants and involve statistical comparison of the intervention to the standard and/or placebo interventions

4. Selection of study design

Clinical research aimed at evaluating traditional medicine should incorporate the conventional concepts of research design, such as randomized controlled trials or other types of clinical studies, such as observational studies. Reference sources which may be used for clinical research design include: The US Food and Drug Administration guidelines: Guidance for industry, The Guideline for Good Clinical Practice produced by the International Conference on Harmonization,as well as the Malaysian Guidelines for Good Clinical Practice.

Conventional concepts of clinical research design may be difficult to apply when using clinical research to evaluate various systems and practices of traditional medicine, Depending on the goal of the assessment. In such circumstances, the choice of study design should be discussed on a case-by-case basis with experienced traditional medical practitioners. The study design may be chosen from a whole spectrum of clinical research designs described below including:

4.1 Single-case design

Single-case designs have the advantage of being adaptable to the clinical needs of the patient and the therapeutic approach of the practitioner, but have limitations due to their lack of generalization to other patients. Such designs are appropriate for the development of research hypotheses, testing those hypotheses in daily clinical practice and refining clinical techniques. Single-case designs using a common protocol (if the protocol can be systematically followed) should be advocated for collaborative research among practitioners from different backgrounds. For example, single-case designs can evaluate the effectiveness of various specialized acupuncture methods in patients with a variety of individual differences. In a single- case design, the patient is his or her own control (sequential analysis). Treatment can be randomized for a patient, rather than the patient being randomized for a treatment.

4.2 Black-box design

The study of traditional herbal medicine can also be undertaken in a "black-box" manner. This means that the treatment and all of its components are delivered as they would be in the usual clinical situation. In this type of study, no component of the treatment "package" is isolated and studied independently. This allows the effectiveness of traditional medicine to be determined either within its own theoretical framework or within that of conventional medicine.

4.3 Ethnographic design

Ethnographic studies that document the social and cultural context in which a traditional practice emanates may be appropriate in situations where there is no available scientific literature or other documentation. These and other qualitative studies can provide baseline information from which hypotheses may be generated, and can lead to further research.

4.4 Observational design

Observational studies collect findings on a therapeutic or prophylactic treatment under routine conditions. The special feature of these studies is that they seek, as far as possible, not to influence the individual doctor-patient relationship with respect to indications, and the selection of and carrying out the treatment. These studies may be conducted with or without a control group. The specific details of the study (e.g. the time and extent of examination for each individual patient, the number of patients involved) and the envisaged methods (e.g. data recording and evaluation) must be adapted to the questions investigated in the study (e.g. safety or appropriate posology). Observational studies have specific advantages in studying aspects of clinical safety. The use of such studies to prove efficacy is limited because bias in patient selection may occur. Nevertheless, the level of evidence on efficacy of traditional medicine can be significantly increased by well-designed observational studies.

5. Study outcome measures

It is essential that the outcome measures chosen be appropriate to the research question. Appropriate outcomes may include quantitative and qualitative outcomes; primary and/or secondary outcomes; and generic and/or highly specific outcomes.

6. Selection of patients

It is essential that the sample represent the target population of patients to which the results would be generalized. Publication of the study requires a clear description of the patients using both traditional (herbal) and conventional terms. The reliability of the categorization/diagnostic criteria used in the study should be considered and stated. The source of the patients under study should be comprehensively described along with details of the recruitment process. The inclusion and exclusion criteria should be completely described and rationalized. Any potential bias in patient selection, recruitment and enrollment should be excluded. Investigators should be aware of any potential errors that may occur when studying herbal medicine out of context and without reference to its traditional theories and concepts.

When the research involves techniques that depend on skills that may differ between practitioners, such research should be conducted by more than one practitioner, whenever possible, in order to increase the generalisability of the results.

7. Sample size

The number of patients in a study needs to be adequate, in order to be able to determine any clinically important differences between the study groups. With respect to the study design, the statistical methods used should be appropriate to the proposed analysis of the study's outcome.

8. Control groups

A well-conducted and controlled clinical trial would provide sufficient evidence to establish a relationship between the use of an herbal medicine or traditional procedure-based therapy and the prevention, diagnosis, improvement of treatment of an illness.

Randomized controlled trials require one or more control groups for purposes of comparison. The selection of control groups depends on the objectives of the study. In the evaluation of traditional (herbal) medicine, a concurrent control group should be used. The control groups may involve (not in order of priority):

- well established treatment
- different doses of the same treatment
- placebo treatment
- full-scale (standard) treatment
- Alternative treatment.

Different controls can be used in clinical trials to answer different questions. The use of a placebo, when possible, is desirable, because it generates evidence of better quality. Placebo-controlled trials are intended to establish whether treatment is valuable over and above what might be achieved by a control treatment, and not whether treatment is valuable at all. Thus, it allows researchers to distinguish specific from non-specific effects of treatment in order to determine whether the additional cost, risk and effort of a specific treatment are worthwhile. It is also important for understanding the mechanism of a treatment. This is true for the evaluation of all drugs. It is not only of academic interest, but is also of practical value, especially for

developing new treatments from traditional ones. However, in some cases, placebo-controlled trials may not be possible and applicable.

It is recommended to compare an herbal medicine with both a well-established treatment and another control group (selected from the list of control groups) to determine whether the herbal medicine is useful in the context of current best practice.

One specific problem in clinical research of traditional medicine is the simultaneous conventional treatment of patients (e.g. cancer patients) in a study. It may not be ethically possible to withdraw the conventional treatment. Therefore, in such cases, the focus of research may be on the additional or supportive effects of traditional medicine. Research on combinations of traditional and conventional medicine should always consider potential therapeutic interactions and side-effects.

9. Randomization

Randomization has been of tremendous value in developing comparable groups to assess therapeutic interventions. It is essential to control various known and even unknown biases. Nevertheless, there are many situations where randomization can be impossible or even unethical. The best way to solve this problem is probably by the proper selection of control treatments.

10. Blind assessment

Blind assessment is a critical component of conventional evaluation of therapeutic interventions. However, in the evaluation of efficacy of traditional procedure-based therapies (such as physical therapy, surgery, acupuncture and manual therapy), it can be difficult, impractical or impossible for the practitioner to be kept ignorant of what treatment the patients are receiving. It is essential that this be noted in the evaluation of the validity of a study and that the judgment on its validity is applied consistently across all systems of conventional and traditional medicine.

Treatment blinding in the evaluation of herbal medicines should adopt the approach of conventional medicines, e.g. using active and control formulations with similar color, taste and weight. However, if the herbal medicine cannot be administered in a predetermined standardized formulation, it will be impossible to keep the treatment blinded. Treatment blinding is also difficult to implement in most types of traditional procedure-based therapies. It is important, however, to reduce any bias introduced by non-blinded treatment by carrying out a blinded assessment of the primary outcomes of the study.

11. Evaluation of quality of life

Traditional medicine may be used not only to prevent, diagnose, improve and treat illness, but also to maintain health and improve the quality of life. For example, traditional medicine may not cure patients with certain illnesses, such as cancer and AIDS, but may help improve their quality of life (QOL). The validated WHO QOL user manual can be used to help evaluate the results of clinical research on herbal medicines and traditional procedure-based therapies.

12 Other issues related to therapeutic interventions

12.1 In both the development of a study protocol to assess traditional medicine and products in its submission for publication or for health-authority approval, the following information regarding study outcomes should be clearly provided:

a) description of the therapeutic intervention;
b) description of the reasons for the selection of the therapeutic intervention
c) description of the rationale for the choice of the study outcomes;
d) description of the outcome measurements, including a review of the validity and reliability of the measurements;
e) a comprehensive protocol for taking the measurements (including how and when the measurements were taken); and
f) a clear statement of which expected outcomes the statistical method was based on.

12.2 The following issues should also be considered:

a) The type of intervention must be clearly defined. In treatment using herbal medicines, this should also include, for example, information on the composition and manufacturing of finished herbal products. In traditional procedure-based therapy, this should include, for example, information on the tools and equipment used.

b) The training, skills and experience of the traditional medical practitioner should be taken into account. Issues concerning the variability of treatment by a single practitioner (intra-practitioner variability) and groups of practitioners (inter- practitioner variability) should be addressed. Ideally, the practitioner's diagnostic ability should be reliable.

c) If the setting is an important component of a treatment, its essential features must be described.

d) The dose, frequency and duration of a treatment must be described completely. "Dose" in traditional procedure-based therapies refers to a variety of attributes related to each episode of the therapy, which may vary markedly between different systems of traditional medicine. In acupuncture, for example, "dose" includes the force of a physical manipulation, duration of each episode of therapy, duration of needled manipulation, the number of repetitions of a procedure, the number of needles used, the depth of stimulation, the needle sensation if elicited, the details of any electrical stimulation including stimulus, frequency, intensity, etc. The "dose" used in any study should be based on the relevant literature and experience of traditional medical practitioners.

e) The duration of follow-up 'should be clearly stated. Its length needs to be appropriate to the treatment carried out. In patients with acute pain, follow-up should be carried out within a 24-hour period. In patients with chronic pain, follow-up of a minimum of several months (e.g. 3-6 months) is desirable.

f) Temporal considerations need to be assessed and noted. The study design should take into account seasonal variations that are important to some traditional medicine systems. It should also contain an appropriate time course to allow the treatment to demonstrate its effectiveness. The number of treatments in a finite period of time needs to be clearly stated.

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