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General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine

World Health Organization
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Contents

Foreword

During the last decade, use of traditional medicine has expanded globally and has gained popularity. It has not only continued to be used for primary health care of the poor in developing countries, but has also been used in countries where conventional medicine is predominant in the national health care system.

With the tremendous expansion in the use of traditional medicine worldwide, safety and efficacy as well as quality control of herbal medicines and traditional procedure-based therapies have become important concerns for both health authorities and the public.

Various practices of traditional medicine have been developed in different cultures in different regions without a parallel development of international standards and appropriate methods for evaluating traditional medicine.

The challenge now is to ensure that traditional medicine is used properly and to determine how research and evaluation of traditional medicine should be carried out. Governments and researchers, among others, are increasingly requesting WHO to provide standards, technical guidance and information on these issues.

Since 1991, WHO has developed and issued a series of technical guidelines such as *Guidelines for the assessment of herbal medicines*; *Research guidelines for evaluating the safety and efficacy of herbal medicines*; and *Guidelines for clinical research on acupuncture*. However, these guidelines are still not sufficient to cover the many challenging issues in the research and evaluation of traditional medicine.

In 1997, with the support of the National Center of Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD, USA, a WHO informal discussion developed draft guidelines for methodology on research and evaluation of traditional medicine. Since then, the draft has been revised four times. The guidelines were finalized at a WHO consultation in April 2000, in Hong Kong, China, with the support of the Government of Hong Kong SAR.

The guidelines focus on the current major debates on safety and efficacy of traditional medicine, and are intended to raise and answer some challenging questions concerning the evidence base. They also clarify certain commonly used but unclear definitions. The guidelines present some national regulations for the evaluation of herbal medicine, and also recommend new approaches for carrying out clinical research, for example, using the WHO *QOL user manual*. The quality of life (QOL) manual was developed by the WHO Programme on Mental Health, and may also be used to evaluate the results of clinical research in traditional medicine.

Although the guidelines have been carefully developed and modified, based on comments received from various experts and national health authorities across the world, there still may be other issues and views that, unintentionally, have

not been included. Unfortunately, it is possible that some experts in the field may not have been consulted, due to WHO's limited budget and time for preparation.

There can be no doubt that the guidelines will achieve their purpose of improving the quality and value of research in traditional medicine. It is anticipated that the guidelines will be revised again in the near future, in response to developments in research in traditional medicine. We therefore welcome all comments and views at any time.

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Introduction

Definitions

Traditional medicine

Traditional medicine has a long history. It is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses. The terms complementary / alternative / non-conventional medicine are used interchangeably with traditional medicine in some countries[a].

General considerations

Practices of traditional medicine vary greatly from country to country, and from region to region, as they are influenced by factors such as culture, history, personal attitudes and philosophy. In many cases, their theory and application are quite different from those of conventional medicine. Long historical use of many practices of traditional medicine, including experience passed on from generation to generation, has demonstrated the safety and efficacy of traditional medicine. However, scientific research is needed to provide additional evidence of its safety and efficacy. In conducting research and evaluating traditional medicine, knowledge and experience obtained through the long history of established practices should be respected.

Despite its existence and continued use over many centuries, and its popularity and extensive use during the last decade, traditional medicine has not been officially recognized in most countries. Consequently, education, training and research in this area have not been accorded due attention and support. The quantity and quality of the safety and efficacy data on traditional medicine are far from sufficient to meet the criteria needed to support its use worldwide. The reasons for the lack of research data are due not only to health care policies, but also to a lack of adequate or accepted research methodology for evaluating traditional medicine. It should also be noted that there are published and unpublished data on research in traditional medicine in various countries, but further research in safety and efficacy should be promoted, and the quality of the research should be improved.

[a] The term complementary and alternative medicine is used in some countries to refer to a broad set of health care practices that are not part of the country's own tradition and are not integrated into the dominant health care system.

The methodologies for research and evaluation of traditional medicine should be based on the following basic principles. On the one hand, the methodologies should guarantee the safety and efficacy of herbal medicines and traditional procedure-based therapies. On the other hand, however, they should not become obstacles to the application and development of traditional medicine. This complex issue has been a concern for national health authorities and scientists in recent years.

The discussion of methodologies for research and evaluation of traditional medicine is divided into two parts: herbal medicines and traditional procedure-based therapies. However, successful treatment is often the consequence of both types of treatment acting synergistically. Thus, the efficacy of traditional medicine has to be evaluated in an integrated manner, taking into account both treatment types. Consequently, efficacy assessment of traditional medicine may be quite different to that of conventional medicine. As traditional medicine relies on a holistic approach, conventional efficacy assessment measures may not be adequate.

Purpose of the guidelines

These guidelines have been developed to improve the situation described above, and to promote the proper use and development of traditional medicine. The specific objectives of the guidelines are to:

- harmonize the use of certain accepted and important terms in traditional medicine;
- summarize key issues for developing methodologies for research and evaluation of traditional medicine;
- improve the quality and value of research in traditional medicine; and
- provide appropriate evaluation methods to facilitate the development of regulation and registration in traditional medicine.

Use of the guidelines

These guidelines cover a wide range of issues and are intended to meet the different situations that exist in various countries and regions of the world. The guidelines can be modified to meet the specific needs of WHO Member States. WHO can provide technical assistance to facilitate such efforts. Where appropriate, a phased approach to the implementation of the guidelines should be considered.

These guidelines are intended to serve as a reference source for researchers, health care providers, manufacturers, traders, and health authorities.

1. Methodologies for research and evaluation of herbal medicines

Traditional medication involves the use of herbal medicines, animal parts and minerals. As herbal medicines are the most widely used of the three, and as the other types of materials involve other complex factors, the guidelines presented in Part 1 concentrate on herbal medicines.

1.1 Definitions

Certain definitions in the field of herbal medicines have been presented in other WHO guidelines: *Guidelines for the assessment of herbal medicines* (see Annex I) and *Research guidelines for evaluating the safety and efficacy of herbal medicines* (see Annex II). In order to make WHO definitions consistent, certain terms have now been redefined. Furthermore, the following definitions have been developed in order to meet the demand for the establishment of standard, internationally accepted definitions to be used in the evaluation and research of herbal medicines.

These definitions may differ from those in regulations in countries where traditional medicine is used. Therefore, these definitions are for reference only.

Herbs
Herbs include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials
Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.

Herbal preparations
Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products
Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture

products to which chemically defined active substances have been added, including synthetic compounds and / or isolated constituents from herbal materials, are not considered to be herbal.

Traditional use of herbal medicines

Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations. Traditional use of herbal medicines refers to the long historical use of these medicines. Their use is well established and widely acknowledged to be safe and effective, and may be accepted by national authorities.

Therapeutic activity

Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses; improvement of symptoms of illnesses; as well as beneficial alteration or regulation of the physical and mental status of the body.

Active ingredients

Active ingredients refer to ingredients of herbal medicines with therapeutic activity. In herbal medicines where the active ingredients have been identified, the preparation of these medicines should be standardized to contain a defined amount of the active ingredients, if adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.

1.2 Botanical verification and quality considerations

The first stage in assuring the quality, safety and efficacy of herbal medicines is identification of the plant species. Botanical verification is necessary. The information required includes the currently accepted Latin binomial name and synonyms, vernacular names, the parts of the plant used for each preparation, and detailed instructions for agricultural production and collection conditions according to the each country's good agricultural practice. A WHO Consultation on Traditional Medicine and AIDS (September 1990) addressed the issues of quality control, safety and efficacy of herbal medicines. Detailed information is presented in Annex III. The WHO *Quality control methods for medicinal plant materials*[1] and *WHO monographs on selected medicinal plants*[2] can be consulted for quality control.

1.3 Research and evaluation of safety and efficacy

Research and evaluation of herbal medicines without a long history of use or which have not been previously researched, should follow WHO's *Research guidelines for evaluating the safety and efficacy of herbal medicines*[3].

For herbal medicines with a well-documented history of traditional use, the following procedures for conducting research and evaluating safety and efficacy may be followed.

Literature review

General

In assessing the safety and/or efficacy of a herbal medicine, whether derived from a single plant or from a defined mixture of plants, the first step involves the evaluation of literature reports. The literature search should include reference books, review articles, systematic surveillance of primary sources, and/or database searches. It should be kept in mind, however, that reference books and review articles might contain inaccurate information. Nevertheless, these sources will cite primary references that can be consulted for in-depth analysis. The search profile used should be recorded, as should details of any references cited, whether or not they are available. The literature search should then be extended to gather information on closely related plant species for chemotaxonomic correlation.

If several investigators publish similar safety and/or efficacy data, they should be accepted as useful indicators. *In vitro* (biochemical or cellular) safety data should be viewed as indicators of potential toxicity, but not as absolute markers. *In vivo* data from animal studies are more indicative of toxicity and may be considered to be safety markers.

For both safety and efficacy, a pharmacological effect observed *in vitro* or in animal models is not necessarily applicable to humans. *In vitro* data usually serve to verify the reported mechanism of action in animals or humans. Such data have to be confirmed by clinical studies. Well-documented reports of pharmacological activity in animals or humans may be viewed as having scientific rationale.

Theories and concepts of systems of traditional medicine

The theories and concepts of prevention, diagnosis, improvement and treatment of illness in traditional medicine historically rely on a holistic approach towards the sick individual, and disturbances are treated on the physical, emotional, mental, spiritual and environmental levels simultaneously. As a result, most systems of traditional medicine may use herbal medicines or traditional procedure-based therapies along with certain behavioural rules promoting healthy diets and habits. Holism is a key element of all systems of traditional medicine. Therefore, when reviewing the literature on traditional medicine (both herbal medicines and traditional procedure-based therapies), the theories and concepts of the individual practice of traditional medicine, as well as the cultural background of those involved, must be taken into account.

Review of safety and efficacy literature

A review of the literature should identify the current level of evidence for the safe and effective use of a herbal medicine. The study design should be evaluated, taking note of, for example, the number of patients, specific diagnosis, dosage, duration of administration, criteria for evaluation (such as improvement of symptoms), absence of simultaneous therapy, and valid statistical analysis.

In cases where traditional use and experience of a herbal medicine in humans have not established its safety and efficacy, new clinical studies will be necessary. If well-known herbal medicines are formulated into a new mixture, however, the requirements for proof of safety and efficacy should take into account the well-established uses of each herbal medicine. Such information may appear in au-

thoritative national documents (such as pharmacopoeias or official guidelines of national authorities) or in highly respected scientific publications. However, it should not be forgotten that new preparative methods may alter the chemical, toxicological and even pharmacological profiles of traditionally used herbal medicines.

Issues related to reviewing literature on clinical trials are presented in Part 3, and should also be consulted.

Safety

Reported and documented side-effects (recorded according to established principles of pharmacovigilance) of a herb or herb mixture, its closely related species, constituents of the herb and its preparations / finished herbal products should be taken into account when decisions are made about the need for new pharmacological or toxicological studies.

The absence of any reported or documented side-effects is not an absolute assurance of safety for herbal medicines. However, a full range of toxicological tests may not be necessary. Tests which examine effects that are difficult or even impossible to detect clinically should be encouraged. Suggested tests include immunotoxicity (e.g. tests for allergic reactions), genotoxicity, carcinogenicity and reproductive toxicity. The discussion presented in Annex III may be used for reference. WHO's *Research guidelines for evaluating the safety and efficacy of herbal medicines* can also be consulted for these as well as for other appropriate toxicity tests (see Annex II).

Only when there is no documentation of long historical use of a herbal medicine, or when doubts exist about its safety, should additional toxicity studies be performed. Where possible, such studies should be carried out *in vitro*. Using *in vitro* tests can reduce the number of *in vivo* experiments. If *in vivo* studies are needed, they are to be conducted humanely, with respect for the animals' welfare and rights. Toxicity studies should be conducted in accordance with generally accepted principles, such as those described in WHO's *Research guidelines for evaluating the safety and efficacy of herbal medicines*[3].

Efficacy

It is important for herbal medicines, and particularly for those made from mixture herbal products, that the requirements for proof of efficacy, including the documentation required to support the indicated claims, should depend on the nature and level of the indications. For the treatment of minor disorders, for nonspecific indications, or for prophylactic uses, less stringent requirements (e.g. observational studies) may be adequate to prove efficacy, especially when the extent of traditional use and the experience with a particular herbal medicine and supportive pharmacological data are taken into account. The level of the evidence and the grading of recommendations must correspond to the nature of the illness to be treated or the nature of the physical or mental function to be influenced and regulated. Definitions of levels of evidence and the grading of recommendations from the USA Agency for Health Care Policy and Research may be used for guidance (see Annex IV). Many other national documents, such as the Australian *Guidelines for levels and kinds of evidence to support claims for therapeutic goods* (see Annex V), could also be used for reference.

The therapeutic alternatives available within the community and the risks of the herbal medicine have to be taken into account. It should be noted that in the case of herbal medicines made from herb mixtures, a therapeutic or scientific rationale must exist for the presence of each herb in the mixture. Research on possible therapeutic effects of herbal medicines made from herb mixtures or specific combinations of herbs, however, needs to be carried out.

Clinical trials

The scope and design of such studies should be based on information on traditional use obtained from official national compendia and relevant literature, or by consultation with traditional medical practitioners.

In the case of a new herbal medicine, a new indication for an existing herbal medicine, or a significantly different dosage form or route of administration, the general principles and requirements for a clinical trial should be very similar to those which apply to conventional drugs (see, for example, WHO's good clinical practice protocols, which are described in Annex VI). In some cases, however, the design of such studies must be adapted to deal with the particularities of herbal medicines.

Well-established, randomized controlled clinical trials provide the highest level of evidence for efficacy. Such studies facilitate the acceptance of herbal medicines in different regions and in people with different cultural traditions. However, methods such as randomization and use of a placebo may not always be possible as they may involve ethical issues as well as technical problems. For example, it may be not possible to have a placebo control if the herbal medicine has a strong or prominent smell or taste, as is the case for products containing certain essential oils. In addition, patients who have been treated previously with the herbal medicine under investigation that has a characteristic organoleptic property, cannot be randomized into control groups. In the case of herbal medicines with a strong flavour, placebo substances with the same flavour may have a similar function. In such cases, it may be advisable to use a low dosage of the same herbal medicine as a control. Alternatively, a positive control, such as well-established treatment, can be used. Other examples of control groups are presented in Part 3.

Observational studies involving large numbers of patients may also be a very valuable tool for the evaluation of herbal medicines. According to the theories and concepts of traditional medicine, as mentioned in Part 1 (section 1.3), the prevention, diagnosis, improvement and treatment of illness is often based on the specific needs of the individual patient. Therefore, single-case studies for the evaluation of efficacy of a herbal medicine should not be ignored. Due to the potential contribution of single-case studies to traditional medicine, a more detailed description of this and other study designs is given in Part 3.

Regulatory requirements of national authorities for evaluating herbal medicines differ from country to country. Many governments have recently developed their own national regulations for traditional medicine. For an extensive review of the regulatory situation in various countries, consult WHO's *Regulatory situation of herbal medicines: a worldwide review*[4].

2. Methodologies for research and evaluation of traditional procedure-based therapies

2.1 Types of traditional procedure-based therapies

Traditional procedure-based therapies are therapies that use various techniques, primarily without the use of medication, to provide health care. They include, for example, acupuncture and related techniques, chiropractic, osteopathy, manual therapies, qigong, tai ji, yoga, naturopathy, thermal medicine, and other physical, mental, spiritual and mind–body therapies.

2.2 Evaluation of safety and efficacy

Theories and concepts

The theories and concepts of the various systems of traditional medicine are very important for the research and evaluation of traditional procedure-based therapies. These are discussed in Part 1 (section 1.3).

Safety

In general, traditional procedure-based therapies are relatively safe, if they are performed properly by well-trained practitioners. But accidents do occasionally occur, most probably when practitioners are not fully trained. Therapies should be performed within accepted parameters, and the indications for a therapy should be evidence based when possible. Serious adverse effects of therapies are rare, but supportive data on adverse effects are not readily available. Accordingly, the evaluation of adverse effects should be considered a priority area for systematic evaluation of safety of these therapies.

One problem in ensuring safety of a therapy is variable quality control in the manufacture of therapy equipment. The most effective safety measures, therefore, are to ensure that the equipment used is of good quality, as well as ensuring that the practitioners who use it have had sound and well supervised theoretical and practical training. These are the appropriate ways to minimize incompetent examination of patients, incorrect diagnoses and errors of technique, and to ensure that patients are properly selected for traditional procedure-based therapy. It should also ensure that the practitioner knows how to deal with accidents when they do occur, and knows how to refer the patient to an appropriate physician if the patient does not respond to therapy or if there is a medical emergency. The WHO *Guidelines on basic training and safety in acupuncture*[5] promote the safe use of acupuncture to prevent adverse effects occurring in patients who have been incorrectly selected for treatment. Similar guidelines could be prepared by

WHO Member States. WHO can provide technical assistance to facilitate such efforts.

Efficacy

Many kinds of traditional procedure-based therapies, such as acupuncture and manual therapies, have already been widely used in health care systems in a number of countries. However, there is an increasing demand to study and evaluate the efficacy of these therapies.

The efficacy of most forms of traditional procedure-based therapies depends heavily upon the proficiency of the practitioners, including their skills and experience. This may partly explain the disparity or inconsistency of results reported by different authors, even though the methodologies of the studies were equally sound. Non-specific effects of the therapy can also contribute to efficacy, but these are difficult to measure or quantify. Therefore, clinical trials and other research methodologies are extremely important in the evaluation of the efficacy of traditional procedure-based therapies (see Part 3).

3. Clinical research

3.1 General considerations

Normally, clinical research of all types of conventional and traditional medicine considers both efficacy and safety, and is conducted according to WHO's guidelines for good clinical practice and the Declaration of Helsinki (see Annex VI). Safety evaluation, however, may not be the main focus of clinical research in traditional medicine, because of the long history of traditional medicine. The information here provides further details to the relevant sections dealing with clinical trials in the assessment of herbal medicines (Part 1) and traditional procedure-based therapies (Part 2).

In addition to evaluating the safety and efficacy of traditional medicine through clinical trials, there may be a number of different objectives when evaluating traditional medicine through clinical research, as when using clinical research to evaluate conventional medicine. Some of the objectives specific to the assessment of traditional medicine through clinical research are to:

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

3.2 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 existing scientific research in the field. Where little or no literature exists, the oral tradition and the source of this tradition need 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 (see Part 1, section 1.3). 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.

3.3 Selection of study design

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. The USA Food and Drug Administration guidelines *Guidance for industry: significant scientific agreement in the review of health claims to conventional foods and dietary supplements*, which introduce several types of clinical studies, could be consulted (see Annex VII). The *Guideline for Good Clinical Practice* produced by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (see Annex VIII), as well as official guidelines from other governmental agencies (such as those in Annex V) may also be a good reference source for clinical research design.

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 (see Part 3, section 3.1). 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 which are suitable for assessing traditional medicine (see Annex VII), including:

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. Treatment can be randomized for a patient, rather than the patient being randomized for a treatment.

Black-box design
The study of traditional 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.

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.

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 question 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.

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.

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 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 enrolment should be excluded. Investigators should be aware of any potential errors that may occur when studying traditional 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 in order to increase the generalizability of the results.

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.

Control groups

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

ment of an illness, provided there is a supporting body of evidence from observational or mechanistic studies.

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 medicine, a concurrent control group should be used. The control groups may involve (not in order of priority):

- well established treatment
- non-treatment
- different doses of the same treatment
- sham or placebo treatment
- full-scale treatment
- minimal 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 (see section on clinical trials in Part 1).

It is preferable to compare a herbal medicine with both a well-established treatment and another control group (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 (see section on black-box design in Part 3).

Randomization

Randomization has been a tremendous advance 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 unethical. The best way to solve this problem is probably by the proper selection of control treatments.

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 judgement on its validity be 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 colour, 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.

Evaluation of quality of life

Traditional medicine is 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. The WHO *QOL user manual,* developed by the WHO Programme on Mental Health, can be used to help evaluate the results of clinical research on herbal medicines and traditional procedure-based therapies (see Annex IX)

Other issues related to therapeutic interventions

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

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

The following issues should also be considered:

- The type of intervention must be clearly defined. In treatment using herbal medicines, this should also include, for example, information on the composi-

tion and manufacturing of finished herbal products. In traditional procedure-based therapy, this should include, for example, information on the tools and equipment used.

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

The information in the *ICH Harmonized tripartite guideline: guideline for Good Clinical Practice* issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is a useful example of the information required (see Annex VIII).

4. Other issues and considerations

4.1 Pragmatic research issues

The infrastructure for research in traditional medicine is significantly less developed than that for conventional medicine. However, there is now an increasing demand that the safety and efficacy of traditional medicine be determined, so that it can be considered by the public. In the development of traditional medicine, it is important that support be given to the establishment of appropriate infrastructure within the academic and other institutions of traditional medicine.

Other pragmatic issues that require consideration include funding, facilities, and involvement of properly trained research personnel and traditional medical practitioners.

Clinical research must be carried out under conditions which ensure adequate safety for the subjects. The institution selected must have adequate facilities, including laboratories and equipment, where necessary, and sufficient clerical, medical and allied health workers to support the study as required. Facilities should be available to meet any emergencies.

If a multicentre study is necessary, this may require a special administrative system to ensure that the study is conducted simultaneously and adequately at different sites by several investigators following the same protocol. It will be necessary to train investigators from different sites to follow the same protocol, and to standardize methods of patient selection, termination of patient participation, administration, and data collection and evaluation. Appropriate consultation about the statistical analysis is necessary during the planning, execution and assessment phases to ensure methodological consistency.

4.2 Ethics

The international ethical guidelines for biomedical research involving human subjects (see Annex VI) should be implemented in each clinical trial. An ethics committee, according to each institution's guidelines should review each trial.

Whenever applicable, rescue treatment may be provided to patients involved in a clinical trial involving the use of a placebo or unproven treatment. Use of the rescue treatment may be a secondary outcome measure.

In some countries and hospitals, there are ethical issues that restrict the use of clinical trials. In some cases, the use of a placebo is even illegal, particularly for patients suffering from certain illnesses, such as cancer. Therefore, clinical trials must always be conducted within the framework of the prevailing law in a given country or state.

4.3 Education and training

All health care providers of traditional medicine should be encouraged and required to have proper training in both traditional and conventional medicine, as their training and skills will affect the safety and efficacy of the treatment. The practitioners' knowledge and skills need to be continuously upgraded to enable them to engage in clinical research within their own individual specialty, if necessary. The WHO *Guidelines on basic training and safety in acupuncture*[5] provides an example of training for all health care providers of acupuncture.

4.4 Surveillance systems

According to the situation of traditional medicine in a particular country, governments may need to establish national surveillance systems at different levels of the health sector to monitor and evaluate any adverse effects of traditional medicine. Knowledgeable researchers and practitioners of traditional medicine should be consulted during the development of such systems.

The evaluation of adverse effects needs to be based on appropriate methods of determining causality. Such methods include instruments to determine adverse events experienced by target groups (patients and practitioners), prospective and retrospective studies to determine adverse effects in specific settings, and post-market surveillance of new devices (both herbal medicines and equipment used in traditional procedure-based therapy) where comprehensive evaluation of any adverse effect is documented.

References

1) World Health Organization. Quality control methods for medicinal plant materials. Geneva, World Health Organization, 1998.

2) World Health Organization. WHO monographs on selected medicinal plants. Vol. I. Geneva, World Health Organization, 1999.

3) World Health Organization Regional Office for the Western Pacific. Research guidelines for evaluating the safety and efficacy of herbal medicines. Manila, World Health Organization Regional Office for the Western Pacific, 1993.

4) World Health Organization. Regulatory situation of herbal medicines: a worldwide review. Geneva, World Health Organization, 1998 (unpublished document WHO/TRM/98.1; available on request from Traditional Medicine (TRM/EDM/HTP), World Health Organization, 1211 Geneva 27, Switzerland).

5) World Health Organization. Guidelines on basic training and safety in acupuncture. Geneva, World Health Organization, 1999 (unpublished document WHO/EDM/TRM/99.1; available on request from Traditional Medicine (TRM/EDM/HTP), World Health Organization, 1211 Geneva 27, Switzerland).

Annexes

Note

The following annexes are adapted from a number of different source materials produced by WHO and other organizations. Therefore any reference in the annexes to other sections or parts refers to the original document and not to this document. Please consult the original documents for more details.

Annex I. Guidelines for the assessment of herbal medicines[a]

Introduction

For the purpose of these guidelines, herbal medicines are defined as follows:

> Finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Plant material includes juices, gums, fatty oils, essential oils, and any other substances of this nature. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant material combined with chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines.
>
> Exceptionally, in some countries herbal medicines may also contain, by tradition, natural organic or inorganic active ingredients which are not of plant origin.

The past decade has seen a significant increase in the use of herbal medicines. As a result of WHO's promotion of traditional medicine, countries have been seeking the assistance of the Organization in identifying safe and effective herbal medicines for use in national health care systems.

In 1991, the Director-General of WHO, in a report to the Forty-fourth World Health Assembly, emphasized the great importance of medicinal plants to the health of individuals and communities. Earlier, in 1978, the Thirty-first World Health Assembly had adopted a resolution (WHA31.33) that called on the Director-General to compile and periodically update a therapeutic classification of medicinal plants, related to the therapeutic classification of all drugs; subsequently, resolution WHA40.33, adopted in 1987, urged Member States to ensure quality control of drugs derived from traditional plant remedies by using modern techniques and applying suitable standards and good manufacturing practices; and resolution WHA42.43, of 1989, urged Member States to introduce measures for the regulation and control of medicinal plant products and for the establishment and maintenance of suitable standards. Moreover, the Interna-

[a] Reproduced from *WHO Expert Committee on specifications for pharmaceutical preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996:178–184 (WHO Technical Report Series, No. 863). These guidelines were finalized at a WHO Consultation in Munich, Germany, 19–21 June 1991.

tional Conference on Primary Health Care, held in Alma-Ata, USSR, in 1978, recommended, *inter alia*, the accommodation of proven traditional remedies in national drug policies and regulatory measures.

In developed countries, a resurgence of interest in herbal medicines has resulted from the preference of many consumers for products of natural origin. In addition, manufactured herbal medicines often follow in the wake of migrants from countries where traditional medicines play an important role.

In both developed and developing countries, consumers and health care providers need to be supplied with up-to-date and authoritative information on the beneficial properties, and possible harmful effects, of all herbal medicines.

The Fourth International Conference of Drug Regulatory Authorities, held in Tokyo in 1986, organized a workshop on the regulation of herbal medicines moving in international commerce. Another workshop on the same subject was held as part of the Fifth International Conference of Drug Regulatory Authorities, held in Paris in 1989. Both workshops confined their considerations to the commercial exploitation of traditional medicines through over-the-counter labelled products. The Paris meeting concluded that the World Health Organization should consider preparing model guidelines containing basic elements of legislation designed to assist those countries wishing to develop appropriate legislation and registration.

The objective of these guidelines is to define basic criteria for the evaluation of quality, safety and efficacy of herbal medicines and thereby to assist national regulatory authorities, scientific organizations and manufacturers to undertake an assessment of the documentation / submissions / dossiers in respect of such products. As a general rule in this assessment, traditional experience means that long-term use as well as the medical, historical and ethnological background of those products shall be taken into account. The definition of long-term use may vary according to the country but should be at least several decades. Therefore, the assessment should take into account a description in the medical / pharmaceutical literature or similar sources, or a documentation of knowledge on the application of a herbal medicine without a clearly defined time limitation. Marketing authorizations for similar products should be taken into account.

Prolonged and apparently uneventful use of a substance usually offers testimony of its safety. In a few instances, however, investigation of the potential toxicity of naturally occurring substances widely used as ingredients in these preparations has revealed previously unsuspected potential for systematic toxicity, carcinogenicity and teratogenicity. Regulatory authorities need to be quickly and reliably informed of these findings. They should also have the authority to respond promptly to such alerts, either by withdrawing or varying the licences of registered products containing suspect substances, or by rescheduling the substances to limit their use to medical prescription.

Assessment of quality

Pharmaceutical assessment

This should cover all important aspects of the quality assessment of herbal medicines. It should be sufficient to make reference to a pharmacopoeia monograph if one exists. If no such monograph is available, a monograph must be supplied and should be set out as in an official pharmacopoeia.

All procedures should be in accordance with good manufacturing practices.

Crude plant material

The botanical definition, including genus, species and authority, should be given to ensure correct identification of a plant. A definition and description of the part of the plant from which the medicine is made (e.g. leaf, flower, root) should be provided, together with an indication of whether fresh, dried or traditionally processed material is used. The active and characteristic constituents should be specified and, if possible, content limits should be defined. Foreign matter, impurities and microbial content should be defined or limited. Voucher specimens, representing each lot of plant material processed, should be authenticated by a qualified botanist and should be stored for at least a 10-year period. A lot number should be assigned and this should appear on the product label.

Plant preparations

Plant preparations include comminuted or powdered plant materials, extracts, tinctures, fatty or essential oils, expressed juices and preparations whose production involves fractionation, purification or concentration. The manufacturing procedure should be described in detail. If other substances are added during manufacture in order to adjust the plant preparation to a certain level of active or characteristic constituents or for any other purpose, the added substances should be mentioned in the manufacturing procedures. A method for identification and, where possible, assay of the plant preparation should be added. If identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances (e.g. “chromatographic fingerprint”) to ensure consistent quality of the preparation.

Finished product

The manufacturing procedure and formula, including the amount of excipients, should be described in detail. A finished product specification should be defined. A method of identification and, where possible, quantification of the plant material in the finished product should be defined. If the identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances (e.g. “chromatographic fingerprint”) to ensure consistent quality of the product. The finished product should comply with general requirements for particular dosage forms.

For imported finished products, confirmation of the regulatory status in the country of origin should be required. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be applied.

Stability
The physical and chemical stability of the product in the container in which it is to be marketed should be tested under defined storage conditions and the shelf-life should be established.

Assessment of safety

This should cover all relevant aspects of the safety assessment of a medicinal product. A guiding principle should be that, if the product has been traditionally used without demonstrated harm, no specific restrictive regulatory action should be undertaken unless new evidence demands a revised risk–benefit assessment.

A review of the relevant literature should be provided with original articles or references to the original articles. If official monograph / review results exist, reference can be made to them. However, although long term use without any evidence of risk may indicate that a medicine is harmless, it is not always certain how far one can rely solely on long-term usage to provide assurance of innocuity in the light of concern expressed in recent years over the long-term hazards of some herbal medicines.

Reported side-effects should be documented according to normal pharmacovigilance practices.

Toxicological studies
Toxicological studies, if available, should be part of the assessment. Literature should be indicated as above.

Documentation of safety based on experience
As a basic rule, documentation of a long period of use should be taken into consideration when assessing safety. This means that, when there are no detailed toxicological studies, documented experience of long-term use without evidence of safety problems should form the basis of the risk assessment. However, even in cases of drugs used over a long period, chronic toxicological risks may have occurred but may not have been recognized. The period of use, the health disorders treated, the number of users and the countries with experience should be specified. If a toxicological risk is known, toxicity data must be submitted. The assessment of risk, whether independent of dose or related to dose, should be documented. In the latter case, the dosage specification must be an important part of the risk assessment. An explanation of the risks should be given, if possible. Potential for misuse, abuse or dependence must be documented. If long-term traditional use cannot be documented or there are doubts on safety, toxicity data should be submitted.

Assessment of efficacy

This should cover all important aspects of efficacy assessment. A review of the relevant literature should be carried out and copies provided of the original articles or proper references made to them. Research studies, if they exist, should be taken into account.

Activity
The pharmacological and clinical effects of the active ingredients and, if known, their constituents with therapeutic activity should be specified or described.

Evidence required to support indications
The indication(s) for the use of the medicine should be specified. In the case of traditional medicines, the requirements for proof of efficacy should depend on the kind of indication. For treatment of minor disorders and for non-specific indications, some relaxation in requirements for proof of efficacy may be justified, taking into account the extent of traditional use. The same considerations may apply to prophylactic use. Individual experiences recorded in reports from physicians, traditional health practitioners or treated patients should be taken into account.

Where traditional use has not been established, appropriate clinical evidence should be required.

Combination products
As many herbal remedies consist of a combination of several active ingredients, and as experience of the use of traditional remedies is often based on combination products, assessment should differentiate between old and new combination products. Identical requirements for the assessment of old and new combinations would result in inappropriate assessment of certain traditional medicines.

In the case of traditionally used combination products, the documentation of traditional use (such as classical texts of Ayurveda, traditional Chinese medicine, Unani, Siddha) and experience may serve as evidence of efficacy.

An explanation of a new combination of well-known substances, including effective dose ranges and compatibility, should be required in addition to the documentation of traditional knowledge of each single ingredient. Each active ingredient must contribute to the efficacy of the medicine.

Clinical studies may be required to justify the efficacy of a new ingredient and its positive effect on the total combination.

Intended use

Product information for the consumer
Product labels and package inserts should be understandable to the consumer or patient. The package information should include all necessary information on the proper use of the product.

The following elements of information will usually suffice:

- name of the product
- quantitative list of active ingredient(s)
- dosage form
- indications
  - dosage (if appropriate, specified for children and the elderly)

- mode of administration
- duration of use
- major adverse effects, if any
- overdosage information
- contraindications, warnings, precautions and major drug interactions
- use during pregnancy and lactation

- expiry date
- lot number
- holder of the marketing authorization.

Identification of the active ingredient(s) by the Latin botanical name, in addition to the common name in the language of preference of the national regulatory authority, is recommended.

Sometimes not all information that is ideally required may be available, so drug regulatory authorities should determine their minimal requirements.

Promotion
Advertisements and other promotional material directed to health personnel and the general public should be fully consistent with the approved package information.

Utilization of these guidelines

These guidelines for the assessment of herbal medicines are intended to facilitate the work of regulatory authorities, scientific bodies and industry in the development, assessment and registration of such products. The assessment should reflect the scientific knowledge gathered in that field. Such assessment could be the basis for future classification of herbal medicines in different parts of the world. Other types of traditional medicines in addition to herbal products may be assessed in a similar way.

The effective regulation and control of herbal medicines moving in international commerce also requires close liaison between national institutions that are able to keep under regular review all aspects of production and use of herbal medicines, as well as to conduct or sponsor evaluative studies of their efficacy, toxicity, safety, acceptability, cost and relative value compared with other drugs used in modern medicine.

Annex II. Research guidelines for evaluating the safety and efficacy of herbal medicines[a]

Definition of terms

Herbal medicine
A plant-derived material or preparation with therapeutic or other human health benefits which contains either raw or processed ingredients from one or more plants. In some traditions materials of inorganic or animal origin may also be present.

Characterizing compound
A natural constituent of a plant part that may be used to assure the identity or quality of a plant preparation, but is not necessarily responsible for the plant's biological or therapeutic activity.

Biological activity
A change in the base-line function of an animal or part of an animal brought about by the administration of a test substance.

Therapeutic activity
An intervention that results in the amelioration of the manifestations of human disease.

Processed plant materials
Plant materials treated according to traditional procedures to improve their safety and / or efficacy, to facilitate their clinical use, or to make medicinal preparations.

Medicinal preparations of plant materials
Medicinal preparations that contain one or more of the following: powdered plant materials, extracts, purified extracts, or partially purified active substances isolated from plant materials. In certain cases, materials of animal or mineral origin may also be included in such preparations.

[a] Adapted from *Research guidelines for evaluation the safety and efficacy of herbal medicines*. Manila, World Health Organization Regional Office for the Western Pacific, 1993:35–40.

Guidelines for toxicity investigation of herbal medicines

These guidelines are intended to indicate the standard methods of non-clinical toxicological studies related to assessing the safety of herbal medicines. Not all tests are necessarily required for each herbal medicine intended for human study.

Acute toxicity test

Animal species

Some regulatory agencies require that at least two species be used, one of them to be selected from rodents and the other from non-rodents.

Sex

In at least one of the species, males and females should be used.

Number of animals

In the case of rodents, each group should consist of at least five animals per sex. In the case of non-rodents, each group should consist of at least two animals per sex.

Route of administration

Ordinarily, the oral route is sufficient as this is the normal route of clinical administration. However, some regulatory agencies suggest in addition a parenteral route of administration.

In cases where it is proposed to administer the herbal preparation to a human subject by the parenteral route, it may be sufficient to use this route alone for animal testing.

Dose levels

A sufficient number of dose levels should be used in rodents to determine the approximate lethal dose. In non-rodents, sufficient dose levels should be used for the observation of overt toxic signs.

Frequency of administration

The test substance should be administered in one or more doses during a 24-hour period.

Observation

Toxic signs and the severity, onset, progression and reversibility of the signs should be observed and recorded in relation to dose and time. As a general rule, the animals should be observed for at least seven to fourteen days.

Animals dying during the observation period, as well as rodents surviving to the end of the observation period should be autopsied.

If necessary, a histopathological examination should be conducted on any organ or tissue showing macroscopic changes at autopsy.

Long-term toxicity test

Animal species

Many regulatory agencies require that at least two species be used, one a rodent and the other a non-rodent.

Sex

Normally, the same number of male and female animals should be used.

Number of animals

In cases of rodents, each group should consist of at least ten males and ten females. In the case of non-rodents, each group should consist of at least three males and three females.

When interim examinations are scheduled, the number of animals should be increased accordingly.

Route of administration

Normally, the expected clinical route of administration should be used.

Administration period

The period of administration of the test substance to animals will depend on the expected period of clinical use. The period of administration of the toxicity study may vary from country to country, according to its individual regulations.

The following table reflects commonly used ranges of administration periods:

Expected period of clinical use	Administration period for the toxicity study
Single administration or repeated administration for less than one week	2 weeks to 1 month
Repeated administration, between one week to four weeks	4 weeks to 3 months
Repeated administration, between one to six months	3 to 6 months
Long-term repeated administration for more than six months	9 to 12 months

As a rule, the test substance should be administered seven days a week. Administration periods for the toxicity study must be recorded in each result.

Dose levels

Groups receiving at least three different dose levels should be used.

One dose level should not cause toxic changes (no-effect dose) and one dose level that produces overt toxic effects should be included. Within this range the addition of at least one more dose may enhance the possibility of observing a dose-response relationship for toxic manifestations. All studies should include a vehicle control group of test animals.

Observations and examinations

Observations and examinations should be performed on the following items (from 1 to 6):

1. ***General signs, body weight and food and water intake***
   For all experimental animals, the general signs should be observed daily and body weight and food intake should be measured periodically. If useful, water intake should also be determined. The frequency of measurements should normally be as follows:
   - Body weight: before the start of drug administration, at least once a week for the first three months of administration and at least once every four weeks thereafter.
   - Food intake: before the start of drug administration, at least once a week for the first three months of administration and at least once every four weeks thereafter. If the test substance is administered mixed in the food, the intake should be measured once a week.
2. ***Haematological examination***
   For rodents, blood samples should be taken before autopsy. For non-rodents, blood samples should be taken before the start of drug administration, at least once during the administration period (for studies of longer than one month), and before autopsy.

   For both haematological and blood chemistry examinations, it is desirable to include as many parameters as possible.
3. ***Renal and hepatic function tests***
   Since the liver and kidneys are the usual organs of metabolism and excretion, potentially toxic agents easily affect them; their functions should be monitored in long-term toxicity studies.

   For rodents, a fixed number of animals from each group should be selected and urinalysis should be performed before the start of drug administration, and at least once during the administration period.
4. ***Other function tests***
   If appropriate, ECG and visual, auditory tests should be performed. For rodents, ophthalmological examination should be performed on a fixed number of animals from each group at least once during the administration period; for non-rodents, examination should be performed on all animals be-

fore the start of drug administration and at least once during the period of administration.

5. Animals found dead during the examination should be autopsied as soon as possible. A macroscopic examination should be made of organs and tissues. In addition, where possible, organ weight measurements and histopathological examinations should be performed in an attempt to identify the cause of death and the nature (severity or degree) of the toxic changes present.

6. In order to maximize the amount of useful information that can be obtained during the administration period, all moribund animals should be sacrificed rather than allowed to die. Prior to sacrifice, clinical observations should be recorded and blood samples collected for haematological and blood chemical analysis. At autopsy, a macroscopic examination of organs and tissues and measurement of organ weights should be recorded. A full histopathological examination should be performed in an attempt to characterize the nature (severity of degree) of all toxic changes.

   All survivors should be autopsied at the end of the administration period or of the recovery period after taking blood samples for haematological (including blood chemistry) examinations; organs and tissues should be examined macroscopically and organ weights measured. Histopathological examinations of the organs and tissues of animals receiving lower dosage should also be performed, if changes are found on gross or macroscopic examination of their organs and tissues of these animals, or if the highest dose group reveal significant changes. On the other hand, histopathological examination of all rodents will further improve the chances of detecting toxicity.

Recovery from toxicity

In order to investigate the recovery from toxic changes, animals that are allowed to live for varying lengths of time after cessation of the period of administration of the test substance, should be examined.

Annex III. Report of a WHO Consultation on Traditional Medicine and AIDS: Clinical Evaluation of Traditional Medicines and Natural Products[a]

Preclinical considerations

The participants discussed a variety of issues related to the preclinical stages in the development of traditional medicines and other natural products for the treatment of AIDS. The major points are summarized below.

Botanical verification

The performance of a clinical trial under controlled conditions requires a constant supply of a product whose botanical identification and characterization can be verified. Lack of assurance of plant species identity is arguably the most serious deficiency of commercial herbal products. If there is no reliable chemical basis for determining identity, and botanical morphology is destroyed during formulation by such processes as powdering and extraction, only independent botanical certification can provide the necessary assurance.

A botanical certification scheme, organized along the lines of the WHO certification scheme for pharmaceutical products, would be an invaluable international stimulus towards botanical quality assurance. Each professional grower / supplier of medicinal plant material would be required to submit to the designated national botanical authority an appropriate sample of the plant, in a state of sufficient integrity to allow physical identification for confirmation of species identity. If appropriate, a certificate would then be issued indicating the currently accepted Latin binomial, and synonyms, with associated authority, and its usual common names, as well as the site and date of harvest of the crop. Professional growers could be registered with the national authority and samples for testing could be collected by trained inspectors or qualified botanists. Plant products with established pharmacological activity would be standardized on the basis of correlation of activity with levels of their known active constituent(s) or with appropriate chemical profiles. The products would also be checked for the presence of "characterizing substances", where applicable, for further confirmation of botanical origin. The part(s) of the plant used to make each preparation should be

[a] Adapted from *Report of a WHO Consultation on traditional medicine and AIDS: clinical evaluation of traditional medicines and natural products*. Geneva, 26–28 September 1990. Geneva, World Health Organization, 1990:5–7 (unpublished document WHO / TRM / GPA / 90.2; available on request from Traditional Medicine (TRM / EDM / HTP), World Health Organization, 1211 Geneva 27, Switzerland).

indicated, as well as detailed instructions for harvesting (e.g. stage of growth), storage and processing, prior to and following formulation.

Pharmacological activity

Before a new drug of known chemical structure is tested in a clinical trial, there must be adequate data from *in vivo* and / or *in vitro* studies to validate its claimed therapeutic efficacy. In the case of known herbal remedies, such evidence may be available from the current practices of traditional health practitioners or from reports in the literature.

Establishing a correlation of pharmacological activity with some component in the plant is an invaluable aid to assuring comparability between preparations of a medicinal plant product. In the case of HIV infection, a number of *in vitro* approaches are available for evaluating antiviral activity. The *in vitro* anti-HIV assay could also lead to a chemical assay for active constituent(s).

Safety

There are several aspects of safety that need to be considered for herbal products that are candidates for a clinical trial. The first requirement is to identify any potential toxicity by undertaking an extensive search of the literature and evaluating performance in preclinical toxicological tests. The range of preclinical tests available for the evaluation of a synthetic drug before beginning clinical trials is well known. What is not known, however, is whether such preclinical tests need to be so extensive for traditional medicines.

The use of traditional plant remedies over a long period of time may provide important information on the pharmacological effects in humans of a particular group of chemical compounds—information that is usually not available when testing begins on a new synthetic drug. Because herbal remedies have often been used for centuries, their preparation having been described in classical texts of traditional medicine, they cannot be considered “new drugs” in the same sense as new drug candidates from the pharmaceutical industry, which are usually pure and well characterized chemical entities, never before used in humans. Testing requirements formulated by regulatory authorities to ensure the safety of “new drugs” are therefore not necessarily applicable to traditional remedies. A more limited range of preclinical toxicological tests may be adequate for traditional remedies. Consideration must also be given to the cost of performing extensive animal toxicological tests in developing countries, particularly where laboratory infrastructure is limited. Further, such tests require time that cannot be justified when no other treatment is available. Thus, limited animal testing of a herbal medicine may be justified by the remedy’s previous use in human disease and the fatal character of AIDS.

Because of time-tested usage, national drug testing policies may permit some herbal remedies to be submitted directly to clinical evaluation without prior preclinical or toxicological tests. Other remedies may need at least some preclinical toxicological testing. The requirements for testing will be determined for each country, by its own authorities, in the context of its own regulations, and on the basis of pertinent scientific data on the herbal preparation and its history of use in humans.

When a traditional remedy results in promising activity, either in a bioassay or a human study, further investigation may yield a chemically defined active principle, which might then be considered a "new drug" that would have to be tested for safety and efficacy as prescribed by drug regulatory authorities. Such active agents, however, would probably be given special ("fast-track") consideration because of the urgent need for new drugs effective against AIDS.

A second safety consideration is the prompt recognition of any toxic events that may occur during the course of a clinical trial. It may be particularly difficult to recognize toxic events during a clinical trial in persons with AIDS because of the large number of organ systems usually involved in the disease state and the presence of secondary disease/opportunistic infections. Thus, adverse side-effects may be masked by the normal progression of AIDS and related diseases and it may be difficult to determine whether a new drug actually accelerates the progress of the disease. It is also possible that the incidence and extent of drug toxicity may be increased in organ systems that are compromised by AIDS or AIDS-related diseases, a problem that even extensive testing in animals may fail to predict.

All patients with AIDS, and particularly those entering clinical trials, must be carefully screened for underlying diseases that may not yet have become clinically important. Such diseases are particularly important when they may compromise either liver or renal function and thus prevent adequate drug elimination. Overall health status must therefore be well characterized at the time that a patient is evaluated for entrance to a study.

Because there is always the possibility of an adverse drug reaction during the testing of a new drug, the study design must include a plan for managing patients who experience some manifestation of drug toxicity. Such problems may be exacerbated in AIDS patients because of their susceptibility to secondary infections, which may require treatment with additional drugs. Additional diseases and the drugs used to treat them increase the likelihood of adverse drug interactions as well as adverse reactions to the drugs themselves. The preclinical plan must address these possibilities.

Clinical considerations

Every clinical trial must be conducted according to a protocol that is written and approved before the study starts. The most satisfactory protocols are those that are designed with the collaborative effort of a team of experts representing various disciplines. The trial protocol should include a justification for the trial, and should clearly define the question that the trial is designed to answer. The study population must also be clearly defined, indicating both inclusion and exclusion criteria and the procedures to be used for recruiting study participants and allocating them to various treatment protocols. Study patients should have confirmed HIV infection, either asymptomatic or early symptomatic; in most cases, children and pregnant or lactating women should be excluded. Patients may be recruited from voluntary testing centres and from clinics treating either AIDS or other sexually transmitted diseases. Appropriate informed consent must be obtained from each patient, and each patient should have the opportunity to receive appropriate counselling. The protocol should define appropriate clinical monitor-

ing to detect toxicity as well as to determine efficacy and a plan to deal with drug toxicity should it occur.

An accurate record must be kept for each patient in the study, which should include documentation of informed consent, a medical history, details of treatment received and succinct reports of all physical examinations, follow-up evaluations and laboratory test results.

Efficacy should be judged on the basis of such defined end-points as specific clinical symptoms or signs, the development of particular opportunistic infections, or defined prognostic laboratory markers. Safety should be monitored on the basis of either symptoms or signs, particular attention being given to end-points that may signal forms of toxicity that might be anticipated. Laboratory indicators of liver, renal, cardiac and haematological toxicity should also be monitored.

Evaluation of the trial should be undertaken using appropriate statistics.

Ideally, the study design should be blind, randomized and placebo-controlled. A crossover design may present problems in interpretation of study results, both because of uncertainty concerning the time course over which a drug may act and because a patient's status may change during the two phases of the study.

Every effort must be made to address the problems concerning preparation, quality control and dose standardization for herbal preparations, and to find a satisfactory placebo.

Recommendations

A place for traditional herbal remedies in the health care system will be established only if recommendations for their use are based on studies that make them credible and acceptable. Thus, studies with herbal medicines must satisfy the same criteria of efficacy and safety as do the drugs that are products of the modern pharmaceutical industry.

In this context, the consultation drew up a series of guidelines for clinical trials with traditional medicine products used in the treatment of AIDS and AIDS-related diseases.

The consultation also made the following recommendations:

1. This report should be given wide distribution so that the guidelines can be readily and immediately applied in countries where potential remedies may exist.

2. The guidelines should be used as the basis for the development of clinical trials for the evaluation of traditional medicines and natural products.

3. WHO should monitor the impact of the use of the guidelines at the country level to determine any needs for revision.

4. A second consultation should be convened in two years' time to revise the guidelines on the basis of experience in their use.

5. The WHO Traditional Medicine Programme, together with the WHO Global Programme on AIDS, should jointly identify appropriate institutions in developing countries where clinical evaluation of traditional medicines and natural products for AIDS could be carried out.

6. Other consultations should be convened by the WHO Traditional Medicine Programme, in collaboration with appropriate WHO programmes, to adapt the guidelines for the clinical evaluation of traditional medicines for other primary disease states that are of concern in developing countries, such as malaria and other parasitic diseases.

Annex IV. Definition of levels of evidence and grading of recommendations

Levels of evidence[a]

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and / or clinical experience of respected authorities

[a] Based on USA Agency for Health Care Policy and Research 1992.

Grading of recommendations[a]

Grade	Recommendation
A (Evidence levels quality Ia, Ib)	Requires at least one randomized controlled trial as part of the body of literature of overall good and consistency addressing the specific recommendation.
B (Evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation.
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and / or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

[a] Based on USA Agency for Health Care Policy and Research 1994.

Annex V. Guidelines for levels and kinds of evidence to support claims for therapeutic goods[a]

Claims based on evidence of traditional use

Traditional medicines are used by some 60% of the world's population and in some countries are extensively incorporated into the public health system. They are based on an extensive history of use, often measured over thousands of years. This history provides an accumulated repository of systematic observation that underpins the use of these traditional medicines.

Traditional use may infer community knowledge of the existence and application of a substance but does not necessarily carry with it any scientific assessment or scrutiny. For many products and substances there has been little quantifiable scientific research undertaken into their mode of action and effect. Evidence of traditional use may be used to support claims for therapeutic goods. The Complementary Medicines Evaluation Committee (CMEC) has adopted the following definition of "traditional use" for regulatory purposes.

Traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose.[b]

In assessing traditional use the context of the claim is important. Most traditional forms of medicine are likely to use a mixture of substances, and certain behavioural rules promoting healthy diets and habits are likely to apply to them. In those cases, holistic principles are part of the therapy. Thus the theories, concepts and cultural context of the therapy need to be considered.

In forming a claim based on traditional use, products and substances that form part of traditional therapies should identify the therapy to which they belong as well as the product description / name and the symptom / indication / condition for which the product or substance is claimed to be beneficial. Traditional therapies are considered to include Traditional Chinese Medicine (TCM), traditional Ayurvedic medicine, traditional western herbal medicine, traditional homeopathic medicine, aromatherapy and other indigenous medicines. Where multi-

[a] Adapted from the *Guidelines for levels and kinds of evidence to support claims for therapeutic goods* produced by the Therapeutic Goods Administration, PO Box 100, Woden ACT 2606, Australia, in April 2000.

[b] Where tradition of use has been recorded as an oral rather than written history, then evidence of such should be obtained from the appropriate practitioner or indigenous group(s), who maintain such a history.

component products are comprised of active ingredients from different traditional therapies, the therapy from which each ingredient is derived needs to be described in the claim.

Modification of the classic formulations in Traditional Chinese Medicine (TCM) and Ayurvedic medicine must be based on the classical theory associated with the therapy and on traditional methods of preparation, in order for these products to make a traditional claim. For example, to meet the criteria for a traditional claim using evidence of traditional use, the overall formulation of a TCM needs to reflect the classical methods of combination. Claims for combinations in Western Herbal formulations must be based on evidence linking the particular formulation (including methods of preparation) with traditional preparations, and must reflect the traditional knowledge about each individual herb in the product.

With respect to multigenerational use of homeopathic medicines, it is recognised that homeopathic medicine represents a special case where the manufacturing process of serial dilution is a major component of the tradition of use of the therapy. Providing that a new substance is prepared according to principles described in (Therapeutic Goods Administration [TGA]-approved) homeopathic pharmacopoeia, and satisfies safety requirements, claims may be assessed on an "evidence of traditional use" basis. Evidence of traditional use includes independent written histories of use in traditional or contemporary homeopathic literature, multigenerational use, homeopathic proving, records of clinical use and records of the set of symptoms provoked by a "crude" substance. Claims made in relation to homeopathic products must be consistent with the homeopathic picture of the remedy or remedies on which the claim is based.

Substances that have been altered significantly in their constituent profile from the classical traditional medicine for which the claim is being made, require scientific evidence in order to substantiate their claimed action.

Combinations of substances, some of which have a history of traditional use, and others which do not but are supported by scientific evidence, may make claims based both on their traditional-use components and the scientific evidence, thus allowing a mixed claim. Should scientific evidence be contrary to the evidence based on traditional use, the claim used must reflect the truth, on balance of the evidence available.

For Listable multi-component products, traditional claims can be based on the evidence of traditional use for the product itself, or on evidence for an individual component or components about which claims are made. However, the dose of the component or components mentioned in the claim must be consistent with the evidence, and the composition and preparation of the product must be consistent with the holistic principles of the tradition about which the claim is made.

What kinds of claims does the evidence support?

As described earlier in these guidelines there are two types of evidence which can be used to support claims on therapeutic goods. These are scientific evidence and evidence based on traditional use of a product or substance.

Claims based on scientific evidence

There are various types of claims based on scientific evidence that can be made; they are generally categorised according to the type of information they convey. Additionally, claims can be ranked in relation to the relative strength of the claim and their likely impact on consumers. These rankings provide a basis for the level of scientific evidence which may be required to support each type of claim.

In Australia, claims that may be made about therapeutic goods are categorised into three levels -high, medium and general. Different levels of evidence are required to support each level of claim. Within these three levels there are several different types of claims that may be made. For simplicity, this approach can be summarised as shown in Table 2. A summary of the definitions of the types of claims is provided at Attachment 1 to these guidelines.

Table 2. Levels and types of claims and the evidence required to support them – based on scientific evidence

Level of claim	**Type of claim**	**Evidence required to support claim**
HIGH[1]	• Treats / cures / manages any disease / disorder. • Prevention of any disease or disorder. • Treatment of vitamin or mineral deficiency diseases.	High level. Registration only – evaluated by the CMEC, MEC (Medicines Evaluation Committee) or the ADEC (Australian Drug Evaluation Committee).
MEDIUM	• Health enhancement[2]. • Reduction of risk of a disease / disorder. • Reduction in frequency of a discrete event. • Aids / assists in the management of a named symptom / disease / disorder. • Relief of symptoms of a named disease or disorder[3].	Medium level. Sponsor must hold the evidence for Listable goods.
GENERAL	• Health maintenance, including nutritional support. • Vitamin or mineral supplementation[4]. • Relief of symptoms (not related to a disease or disorder)[3].	General level. Sponsor must hold the evidence for Listable goods.

Notes:

[1] There are some specific exemptions to this table which are not considered to be high level claims. These are shown in Attachment 2 to these guidelines.

[2] Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.

[3] All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".

[4] Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25 percent of the Recommended Dietary Intake (RDI) for that vitamin or mineral. Where vitamins or minerals are the subject of other kinds of claims, the dose must be consistent with the evidence to support the claim being made. Claims should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level.

There is a wide variety of references, research papers and texts which may be used as sources of evidence to support these claims. No list of acceptable references can be exhaustive, but some broad guidance for sponsors is offered in Attachment 3 to these guidelines. The absence of a reference from this list does not necessarily mean the reference is unsuitable for inclusion.

Sponsors should make sure that the research on which they rely is relevant to the specific product being promoted and to the specific benefit being claimed. Further guidance for Registrable products is available in the Australian Guidelines for the Registration of Drugs (volume 2) for OTC products, and for complementary medicines, the Australian Guidelines for Complementary Medicines (currently in draft form).

Registrable diseases list

There is a list of diseases / disorders about which claims may be made only after evaluation of the product and the claim(s) through Registration of the product. The list refers to serious diseases / disorders and it applies to claims based on evidence of traditional use, as well as to those based on scientific evidence. The list is known as the "Registrable disease" list and it applies to medicines but not devices. Decisions made with respect to the Registration of medical devices are based on a different set of categorisations and guidelines.

The definition of a serious disease or disorder is one for which there is a substantial body of medical opinion that the disease cannot or should not be diagnosed or treated except under medical advice.

Claims for Registrable diseases may be made under certain circumstances, but only after the safety, quality and efficacy of the product and the claim(s), have been evaluated by the CMEC or other relevant evaluation committee. Where a sponsor seeks to mention a Registrable disease in what would otherwise have been categorised as a medium or general level claim, that claim would become Registrable and the product would require Registration (that is, evaluation by the TGA with the advice of the CMEC, MEC, or ADEC). The "Registrable disease" list is shown in Table 3.

Table 3. The Registrable disease list (for medicines)

Disease/disorder/action – serious manifestation of	**Disease/disorder/action – serious manifestation of (cont'd)**
Abortifacient action.	Infectious diseases, including sexually transmitted diseases, but not: • symptomatic relief of upper respiratory tract infections; • management of cold sores; • the use of condoms to prevent transmission during sexual intercourse; or • topical treatment for non genital warts.
Cardiovascular diseases but not: • the use of devices to measure parameters or control circulation locally; or • reference to assistance of peripheral circulation.	Insomnia, persistent.
Dental and periodontal disease but not • dental caries.	Mental diseases, ailments or defects, including substance abuse.
Diseases of joint, bone, collagen, and rheumatic disease, but not • relief of symptoms; • osteoarthritis, or • calcium for the prevention of osteoporosis.	Metabolic disorders.
Diseases of the eye or ear likely to lead to severe impairment, blindness or deafness.	Musculoskeletal diseases.
Diseases of the liver, biliary system or pancreas, but not: ▪ liver tonic or liver formula.	Neoplastic disease (all cancers).
Endocrine diseases and conditions, including diabetes and prostatic disease, but not: ▪ pregnancy testing.	Nervous system diseases, but not • folate for neural tube defects.
Gastrointestinal diseases or disorders, but not • relief of symptoms.	Renal diseases and diseases of the genito-urinary tract.
Haematological disorders and diseases.	Respiratory diseases, but not: ▪ symptomatic relief of upper respiratory tract infections.
Immune disorders and diseases.	Skin diseases, other than relief of symptoms by topical treatment, with a warning not to use for long periods without medical advice. Sunscreens may however, carry claims relating to the prevention of skin cancer and skin damage.

Other:	
Immunisation	Poisoning, venomous bites and stings – treatment of.

The CMEC is in the process of developing a guideline to support the interpretation of the Registrable diseases list. The guideline identifies those diseases / disorders that may be mentioned in claims on Listed goods, and therefore claims relating to these diseases / disorders do not, in general, require Registration. TGA advice may be sought where sponsors are in doubt about diseases / disorders that are not included in either list. The first draft of such a guideline (The Listable disease list) is at Attachment 4 to this document.

Claims based on evidence of traditional use

In Australia claims which may be made about therapeutic goods using evidence of traditional use are categorised into two levels—medium and general—according to the relative strength of the claim. Medium level claims are stronger claims but their wording is required to be qualified and more evidence is required to support them. This general approach is summarised in Table 4. Specific approaches have been developed for homeopathic and aromatherapy products. These approaches are summarised in Tables 5 and 6 respectively. A summary of the definitions of the types of claims is provided at Attachment 1 to these guidelines.

Table 4. Levels and types of claims and the evidence required to support them - based on evidence of traditional use

Level of claim	Type of claim	Wording of Claim [2]	Evidence required to support claim
MEDIUM	• Health enhancement [1] • Reduction of risk of a disease / disorder. • Reduction in frequency of a discrete event. • Aids / assists in the management of a named symptom / disease / disorder. • Relief of symptoms of a named disease or disorder.[5,6]	This (tradition) medicine has been used for (indication)[5]. This claim is based on traditional use[3].	Primary evidence : Two of the following four sources that demonstrate adequate support for the indications claimed: 1. TGA-approved Pharmacopoeia. 2. TGA approved Monograph. 3. Three independent written histories of use in the classical or traditional medical literature[4]. 4. Availability through any country's government public dispensaries for the indication claimed.

Notes:

[1] Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.

[2] Or words to this effect

[3] Where scientific evidence is available to support the entire claim, the words, "This claim is based on traditional use" is optional.

[4] In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts that accurately report the classical or traditional literature may be used to support claims.

[5] Terms must be in the original language of the traditional medical culture, for example "Shen" not "Kidney" in TCM.

[6] All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".

Table 4. Levels and types of claims and the evidence required to support them - based on evidence of traditional use (cont'd)

Level of claim	Type of claim	Wording of Claim[1]	Evidence required to support claim
GENERAL	• Health maintenance, including for example claims relating to nutritional support. • Relief of symptoms (not referring to a disease or disorder)[2]. • Claims for traditional syndromes and actions [3].	This (tradition) medicine has been traditionally used for (indication)[3].	Primary evidence: One of the following four sources that demonstrates adequate support for the indications claimed: 1. TGA-approved Pharmacopoeia. 2. TGA-approved Monograph. 3. Three independent written histories of use in the classical or traditional medical literature [4]. 4. Availability through any country's government public dispensaries for the indication claimed.

Notes:

[1] Or words to this effect.

[2] All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".

[3] Terms must be in the original language of the traditional medical culture, for example "Shen" not "Kidney" in TCM.

[4] In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts that accurately report the classical or traditional literature may be used to support claims.

Table 4. Levels and types of claims and the evidence required to support them - based on evidence of traditional use (cont'd) - non-primary evidence

Supporting evidence	Commonly referred to in appropriate prescribed teaching textbooks used in tertiary-level training of healthcare professionals. This evidence does not stand alone and may only be used in conjunction with primary evidence.

Annex VI. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products[a]

Ethical principles

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki (see Appendix 1). Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) or non-maleficence (doing no harm), as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects or the laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles (see sections 3 and 4).

Declaration of Helsinki

The current revision of the Declaration of Helsinki (Appendix 1) is the accepted basis for clinical trial ethics, and must be fully followed and respected by all parties involved in the conduct of such trials. Any departures from the Declaration must be justified and stated in the protocol. Independent assurance that subjects are protected can be provided only by an ethics committee and freely obtained informed consent.

Ethics committee

The role of the ethics committee (or other board responsible for reviewing the trial) is to ensure the protection of the rights and welfare of human subjects participating in clinical trials, as defined by the current revision of the Declaration of Helsinki and national and other relevant regulations, and to provide public reassurance, *inter alia*, by previewing trial protocols, etc. (see section 2).

The ethics committee should be constituted and operated so that its tasks can be executed free from bias and from any influence of those who are conducting the trial.

The ethics committee should have documented policies and procedures as a basis for its work, which should be available to the public. These should set out the authority under which the committee is established, the number of members elected and their qualifications, a definition of what it will review, and its authority to intervene and maintain records of its activities. The documents should also

[a] Adapted from *The use of essential drugs. Eighth list*. Geneva, World Health Organization, 1995:106–107;108–110 (WHO Technical Report Series, No. 850).

state how frequently the committee will meet and how it will interact with the investigator and/or sponsor.

The investigator, or the investigator and the sponsor, must consult the relevant ethics committee(s) regarding the suitability of a proposed clinical trial protocol (including appendices and amendments) and of the methods and materials to be used in obtaining and documenting the informed consent of the subjects.

The ethics committee has an ongoing responsibility for the ethical conduct of research, and therefore must be informed of all subsequent amendments to the protocol and of any serious adverse events occurring during the trial, or other new information likely to affect the safety of the subjects or the conduct of the trial. The ethics committee should be consulted if a re-evaluation of the ethical aspects of the trial appears to be required, or if there is any doubt regarding the importance of a protocol change or new information.

Subjects must not be entered into the clinical trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures. The ethics committee should give its opinion and advice in writing within a reasonable time, clearly identifying the trial protocol, itemizing the documents studied and stating the date of review. A list of those present at the committee meeting, including their professional status, should be attached.

When reviewing a clinical trial proposal, the ethics committee should consider the following:

(a) The acceptability of the investigator for the proposed trial, on the basis of sufficient information made available to the committee, in terms of his or her qualifications, experience, availability for the duration of the trial, supporting staff and available facilities.

(b) The suitability of the protocol, including the objectives of the study and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others, and the efficiency of its design, i.e. the potential for reaching sound conclusions with the smallest possible exposure of subjects.

(c) The means by which trial subjects will be recruited, necessary or appropriate information will be given, and consent will be obtained. This is particularly important in the case of trials involving subjects who are members of a group with a hierarchical structure or another vulnerable group (see section 3.3, (c)–(f)).

(d) The adequacy and completeness of the information, which should be written in a language and at a level of complexity understandable to everyone involved, to be given to the subjects, their relatives, guardians or, if necessary, legal representatives. All such written information must be submitted in its final form to the ethics committee.

(e) Provision, if any, for compensation or treatment in the case of death or other loss or injury of a subject, if attributable to a clinical trial, and details of any insurance or indemnity (a source of legal and financial support) to cover the liability of the investigator(s) and sponsor (see section 5.9).

(f) The appropriateness of the extent and form of payment through which the sponsor will remunerate or compensate the organization(s) and/or investigator(s) conducting the trial and the trial subjects, as required by local laws and regulations.

(g) The acceptability of any proposed amendments to the protocol that are likely to affect the safety of the subjects or the conduct of the trial.

Annex VII. Guidance for industry: significant scientific agreement in the review of health claims for conventional foods and dietary supplements[a]

Identifying data for review

The first step in preparing or reviewing a health claim petition is to identify all relevant studies.

The types of studies considered in a health claim review include human studies and frequently also include "pre-clinical" evidence, e.g., *in vitro* laboratory investigations and other mechanistic studies. Studies of humans can be divided into two types: interventional studies and observational studies.

In an interventional study, the investigator controls whether the subjects receive an exposure or an intervention whereas in an observational study, the investigator does not have control over the exposure or the intervention. In general, interventional studies provide the strongest evidence for an effect.

Regardless of the inherent strengths and weaknesses of a study design, the overall quality and relevance of each individual study is paramount in assessing its contribution to the weight of the evidence for the proposed substance/disease relationship.

Interventional studies

The "gold standard" of interventional studies is the randomized controlled clinical trial.

In a randomized controlled trial, subjects similar to each other are randomly assigned either to receive the intervention or not to receive the intervention. As a result, subjects who are most likely to have a favorable outcome independent of any intervention are not preferentially selected to receive the intervention being studied (selection bias). Bias may be further reduced if the researcher who assesses the outcome does not know which subjects received the intervention (blinding). Randomized controlled clinical trials are not an absolute requirement to

[a] Reproduced from *Guidance for industry: significant scientific agreement in the review of health claims for conventional foods and dietary supplements* issued 22 December 1999 by the USA Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Federal building 8, 200 C Street, SW, Washington, DC 20204, USA.

demonstrate significant scientific agreement in all cases, but are considered the most persuasive and given the most weight. A single large, well-conducted and controlled clinical trial could provide sufficient evidence to establish a substance/disease relationship, provided that there is a supporting body of evidence from observational or mechanistic studies.

Observational studies

There is no universally valid method for weighing categories of observational studies. However, in general, observational studies include, in descending order of persuasiveness, cohort (longitudinal) studies, case-control studies, cross-sectional studies, uncontrolled case series or cohort studies, time-series studies, ecological or cross-population studies, descriptive epidemiology, and case reports.

Observational studies may be prospective or retrospective. In prospective studies, investigators recruit subjects and observe them prior to the occurrence of the outcome. In retrospective studies, investigators review the records of subjects and interview subjects after the outcome has occurred. Retrospective studies are usually considered to be more vulnerable to recall bias (error that occurs when subjects are asked to remember past behaviors) and measurement error but are less likely to suffer from the subject selection bias that may occur in prospective studies.

- Cohort studies compare the outcome of subjects who have received a specific exposure with the outcome of subjects who have not received that exposure.
- In case-control studies, subjects with the disease are compared to subjects who do not have the disease (control group). Subjects are enrolled based on their outcome rather than based on their exposure.
- In cross-sectional studies, at a single point in time the number of individuals with a disease who have received a specific exposure is compared to the number of individuals without the disease who did not receive the exposure.
- Uncontrolled case series studies depict outcomes in a group without comparing to a control group.
- Time-series studies compare outcomes during different time periods, e.g. whether the rate of occurrence of a particular outcome during one five-year period changed during a subsequent five-year period.
- In ecological studies, the rate of a disease is compared across different populations. Investigators seek to identify population traits that may cause the disease.
- Descriptive epidemiology refers to study designs that assess parameters related to the frequency and distribution of disease in a population, such as the leading cause of death.
- Case reports describe observations of a single subject or a small number of subjects.

Research synthesis studies

"Research synthesis" studies, including meta-analyses, may be useful as supporting evidence for a health claim, but any role beyond this function is as yet unresolved.

The appropriateness of research synthesis studies to establish substance/disease relationships is not known. This is especially true when observational data are entered into meta-analyses. Discussions on the topic have been published[1–4], and there are on-going efforts to identify criteria and critical factors to consider in both conducting and using such analyses, but standardization of this methodology is still emerging. Therefore, in general, such analyses serve as supporting evidence rather than as primary evidence. To date, while meta-analyses have been reviewed as part of the health claim authorization process, no health claims have been authorized on the basis of meta-analysis studies alone.

References

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4) Hasselblad V, Mosteller F, Littenberg B, Chalmers TC, Hunick MG, Turner JA, et al. A survey of current problems in meta-analysis. Discussion from the Agency for Health Care Policy and Research Inter-PORT Work Group on Literature Review / Meta-Analysis. Medical Care 1995;33:202–220.

Annex VIII. Guideline for Good Clinical Practice[a]

Clinical trial protocol and protocol amendment(s)

General information

1. Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

2. Name and address of the sponsor and monitor (if other than the sponsor).

3. Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

4. Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

5. Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6. Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

7. Name(s) and address(es) of the clinical laboratory(ies) and other medical and / or technical department(s) and / or institutions involved in the trial.

Background information

1. Name and description of the investigational product(s).

2. A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

3. Summary of the known and potential risks and benefits, if any, to human subjects.

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[a] Adapted from the *ICH Harmonized tripartite guideline: guideline for Good Clinical Practice* issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, International Federation of Pharmaceutical Manufacturers Associations, PO Box 9, 1211 Geneva, Switzerland. Recommended for adoption on 1 May 1996 by the ICH Steering Committee.

4. Description of, and justification for, the route of administration, dosage, dosage regimen, and treatment period(s).

5. A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6. Description of the population to be studied.

7. References to literature and data that are relevant to the trial, and that provide background for the trial.

Trial objectives and purpose

A detailed description of the objectives and the purpose of the trial.

Trial design

1. The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

   A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

2. A description of the type / design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

3. A description of the measures taken to minimize / avoid bias, including:

   (a) randomization

   (b) blinding.

4. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

5. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6. A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial and entire trial.

7. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

8. Maintenance of trial treatment randomization codes and procedures for breaking codes.

9. The identification of any data to be recorded directly on the case report forms (i.e. no prior written or electronic record of data), and to be considered to be source data.

Selection and withdrawal of subjects

1. Subject inclusion criteria.

2. Subject exclusion criteria.

3. Subject withdrawal criteria (i.e. terminating investigational product treatment / trial treatment) and procedures specifying:

   (a) when and how to withdraw subjects from the trial / investigational product treatment;

   (b) the type and timing of the data to be collected for withdrawn subjects;

   (c) whether and how subjects are to be replaced;

   (d) the follow-up for subjects withdrawn from investigational product treatment / trial treatment.

Treatment of subjects

1. The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route / mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment / trial treatment group / arm of the trial.

2. Medication(s) / treatment(s) permitted (including rescue medication) and not permitted before and / or during the trial.

3. Procedures for monitoring subject compliance.

Assessment of efficacy

1. Specification of the efficacy parameters.

2. Methods and timing for assessing, recording, and analysing of efficacy parameters.

Assessment of safety

1. Specification of safety parameters.

2. The methods and timing for assessing, recording, and analysing safety parameters.

3. Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

4. The type and duration of the follow-up of subjects after adverse events.

Statistics

1. A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

2. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

3. The level of significance to be used.

4. Criteria for the termination of the trial.

5. Procedure for accounting for missing, unused, and spurious data.

6. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and / or in the final report, as appropriate).

7. The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

Direct access to source data/documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s) / institution(s) will permit trial-related monitoring, audits, institutional review board / independent ethics committee review, and regulatory inspection(s), providing direct access to source data / documents.

Quality control and quality assurance

Ethics

Description of ethical considerations relating to the trial.

Data handling and record keeping

Financing and insurance

Financing and insurance if not addressed in a separate agreement.

Publication policy

Publication policy, if not addressed in a separate agreement.

ANNEX IX. WHO QOL (quality of life) user manual: facet definitions and response scales[a]

Introduction

Each WHOQOL facet can be characterised as a description of a behaviour, a state of being, a capacity or potential or a subjective perception or experience. For example, pain is a subjective perception or experience; fatigue may be defined as a state; mobility may be defined either as a capacity (ability to move around) or as a behaviour (actual report of walking). A definition was written for each of the facets of quality of life covered by the WHOQOL assessment.

Overall Quality of Life and Health

These questions examine the ways in which a person assesses his/her overall quality of life, health and well-being.

DOMAIN I - PHYSICAL DOMAIN

1. Pain and discomfort

This facet explores unpleasant physical sensations experienced by a person and, the extent to which these sensations are distressing and interfere with life. Questions within the facet include the control the person has over the pain and the ease with which relief from pain can be achieved. The assumption is made that the easier the relief from pain, the less the fear of pain and its resulting effect on quality of life. Similarly changes in levels of pain may be more distressing than pain itself. Even when a person is not actually in pain, either through taking drugs or because the pain is by its very nature on and off (e.g. migraine), his/her quality of life may be affected by the constant threat of pain. It is acknowledged that people respond to pain differently, and differing tolerance and acceptance of pain is likely to affect its impact on quality of life.

Unpleasant physical sensations such as stiffness, aches, long-term or short-term pain, or itches are included. Pain is judged to be present if a person reports it to be so, even if there is no medical reason to account for it.

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[a] Reproduced from *WHOQOL user manual*. Geneva, World Health Organization, 1998:61–71 (unpublished document WHO/MNH/MHP/98.3; available on request from Programme on Mental Health, World Health Organization, 1211 Geneva 27, Switzerland).

2. Energy and fatigue

This facet explores the energy, enthusiasm and endurance that a person has in order to perform the necessary tasks of daily living, as well as other chosen activities such as recreation. This may extend from reports of disabling tiredness to adequate levels of energy, to feeling really alive. Tiredness may result from any one of a number of causes, for example illness, problems such as depression, or over-exertion.

The impact of fatigue on social relationships, the increased dependence on others due to chronic fatigue and the reason for any fatigue are beyond the scope of questioning, although they are implicit to the questions in this facet and facets concerned specifically with daily activities and interpersonal relationships.

3. Sleep and rest

This facet concerns how much sleep and rest, and problems in this area, affect the person's quality of life. Sleep problems might include difficulty going to sleep, waking up during the night, waking up early in the morning and being unable to go back to sleep and lack of refreshment from sleep.

The facet's focus is on whether sleep is disturbed or not; this can be for any reason, either to do with the person or to do with the environment.

The questions in this facet do not inquire into specific aspects of sleep such as waking up early in the morning or whether or not a person takes sleeping pills. The question of whether a person is dependent on substances (e.g. sleeping pills) to help him / her sleep is covered in a separate facet.

DOMAIN II - PSYCHOLOGICAL

4. Positive feelings

This facet examines how much a person experiences positive feelings of contentment, balance, peace, happiness, hopefulness, joy and enjoyment of the good things in life. A person's view of, and feelings about the future are seen as an important part of this facet. For many respondents this facet may be regarded as synonymous with quality of life. Negative feelings are not included as these are covered elsewhere.

5. Thinking, learning, memory and concentration

This facet explores a person's view of his / her thinking, learning, memory, concentration and ability to make decisions. This incorporates the speed of thinking and clarity of thought. Questions disregard whether a person is alert, aware or awake, even though these underlie thinking, memory and concentration. It is acknowledged that some people with cognitive difficulties may have no insight into their difficulties, and in these cases proxy evaluations may be a necessary addition to the person's subjective evaluation. A similar problem may be a reluctance to admit to problems in this area among some respondents.

6. Self-esteem

This facet examines how people feel about themselves. This might range from feeling positive about themselves to feeling extremely negative about themselves. A person's sense of worth as a person is explored. The aspect of self esteem concerned with a person's feeling of self-efficacy, satisfaction with oneself and control is also included in the focus of this facet.

Questions are likely to include people's feelings about themselves in a range of areas: how they are able to get along with other people; their education; their appraisal of their ability to change or accomplish particular tasks or behaviours; their family relations; and their sense of dignity and self-acceptance. To some people self-esteem depends largely on how they function, whether at work, at home or how they are perceived and treated by others. In some cultures self-esteem is the esteem felt within the family rather than individual self-esteem. It is assumed that questions will be interpreted by respondents in ways that are meaningful and relevant to their position in life.

Questions do not include specific references to body image and social relationships as these are covered in different areas. However, the sense of self-worth that comes from these areas is intended to be covered by the questions though at a more general level. It is acknowledged that some people may find self-esteem difficult to talk about, and questions are framed trying to take this into account.

7. Body image and appearance

This facet examines the person's view of his / her body. Whether the appearance of the body is seen in a positive or negative way is included in this facet. The focus is on the person's satisfaction with the way he / she looks and the effect it has on his / her self-concept. This includes the extent to which "perceived" or actual bodily impairments, if present, can be corrected (e.g. by make-up, clothing, artificial limbs, etc.).

How others respond to a person's appearance is likely to affect the person's body image very considerably. The phrasing of the questions aims to encourage respondents to answer how they really feel rather than how they feel they should respond. In addition they are phrased so as to be able to include a person who is happy with the way they look as well as someone who is severely physically handicapped.

8. Negative feelings

This facet concerns how much a person experiences negative feelings, including despondency, guilt, sadness, tearfulness, despair, nervousness, anxiety and a lack of pleasure in life. The facet includes a consideration of how distressing any negative feelings are and their impact on the person's day-to-day functioning. Questions are framed so as to include people with quite disabling psychological difficulties such as severe depression, mania or panic attacks.

Questions do not include poor concentration, nor the relationship between negative affect and the person's social relationships because these are covered elsewhere. Nor do questions include any detailed assessment of the severity of the negative feelings.

DOMAIN III - LEVEL OF INDEPENDENCE

9. Mobility

This facet examines the person's view of his / her ability to get from one place to another, to move around the home, move around the work place, or to and from transportation services.

The focus is on the person's general ability to go wherever he / she wants to go without the help of others regardless of the means used to do so. The assumption is made that wherever a person is dependent to a significant extent for his / her mobility on another person this is likely to affect quality of life adversely. In addition, questions address people with mobility difficulties regardless of whether changes in their mobility were sudden or more gradual although it is acknowledged that this is likely to affect the impact on quality of life significantly.

A person's impairment does not necessarily affect his / her mobility. So for example someone using a wheelchair or walking frame may have satisfactory mobility in an adequately adapted home or workplace. Nor does this facet include transportation services (e.g. car, bus) as this is covered in a separate facet (Transport).

10. Activities of daily living

The facet explores a person's ability to perform usual daily living activities. This includes self-care and caring appropriately for property. The focus is on a person's ability to carry out activities, which he / she is likely to need to perform on a day-to-day basis. The degree to which people are dependent on others to help them in their daily activities is also likely to affect their quality of life.

The questions do not include aspects of daily living which are covered in other areas; namely, specific activities affected by fatigue, sleep disturbances, depression, anxiety, mobility, and so on. Questions disregard whether a person has a home or a family.

11. Dependence on medication or treatments

This facet examines a person's dependence on medication or alternative medicines (such as acupuncture and herbal remedies) for supporting his / her physical and psychological well-being. Medications may in some cases affect a person's quality of life in a negative way (e.g. side-effects of chemotherapy) whilst in other cases it may enhance the person's quality of life (e.g. cancer patients using pain killers).

This facet includes medical interventions that are not pharmacological but on which the person is still dependent, for example a pacemaker, artificial limb or colostomy bag. The questions do not include detailed enquiry into the type of medication.

12. Working capacity

This facet examines a person's use of his or her energy for work. "Work" is defined as any major activity in which the person is engaged. Major activities might

include paid work, unpaid work, voluntary community work, full-time study, care of children and household duties. Because such questions refer to these possible types of major activities, the facet focuses on a person's ability to perform work, regardless of the type of work.

The questions do not include how people feel about the nature of the work that they do, nor do they include the quality of their work environment.

DOMAIN IV - SOCIAL RELATIONSHIPS

13. Personal relationships

This facet examines the extent to which people feel the companionship, love and support they desire from the intimate relationship(s) in their life. This facet also addresses commitment to and current experience of caring for and providing for other people.

This facet includes the ability and opportunity to love, to be loved and to be intimate with others both emotionally and physically. The extent to which people feel they can share moments of both happiness and distress with loved ones, and a sense of loving and being loved are included. The physical aspects of intimacy such as hugging and touch are also included. It is acknowledged, however, that this facet is likely to overlap considerably with the intimacy of sex that is covered in the facet Sexual activity.

The questions include how much satisfaction a person gets from, or has problems managing the burdens of caring for others. The possibility of this being both a positive as well as a negative experience is implicit to the facet.

This facet addresses all types of loving relationships, such as close friendships, marriages and both heterosexual and homosexual partnerships.

14. Social support

This facet examines how much a person feels the commitment, approval and availability of practical assistance from family and friends. Questions explore how much family and friends share in responsibility and work together to solve personal and family problems. The facet's focus is on how much the person feels he / she has the support of family and friends, in particular to what extent he / she might depend on this support in a crisis.

This includes how much the person feels he / she receives approval and encouragement from family and friends. The potentially negative role of family and friends in a person's life is included in this facet and questions are framed to allow negative effects of family and friends such as verbal and physical abuse to be recorded.

15. Sexual activity

This facet concerns a person's urge and desire for sex, and the extent to which the person is able to express and enjoy his / her sexual desire appropriately.

Sexual activity and intimacy are for many people intertwined. Questions, however, enquire only about sex drive, sexual expression and sexual fulfilment, with other forms of physical intimacy being covered elsewhere. In some cultures fertility is central to this facet, and child bearing is an extremely valued role. This facet incorporates this aspect of sex in these cultures, and is likely to be interpreted in these terms in these cultures. Questions do not include the value judgements surrounding sex, and address only the relevance of sexual activity to a person's quality of life. Thus the person's sexual orientation and sexual practices are not seen as important in and of themselves: rather it is the desire for, expression of, opportunity for and fulfilment from sex that is the focus of this facet.

It is acknowledged that sexual activity is difficult to ask about, and it is likely that responses to these questions in some cultures may be more guarded. It is further anticipated that people of different ages and different gender will answer these questions differently. Some respondents may report little or no desire for sex without this having any adverse effects on their quality of life.

DOMAIN V - ENVIRONMENT

16. Physical safety and security

This facet examines the person's sense of safety and security from physical harm. A threat to safety or security might arise from any source such as other people or political oppression. As such this facet is likely to bear directly on the person's sense of freedom. Hence, questions are framed to allow answers that range from a person having the opportunities to live without constraints, to the person living in a state or neighbourhood that is oppressive and felt to be unsafe.

Questions include a sense of how much the person thinks that there are "resources" which protect or might protect his / her sense of safety and security. This facet is likely to have particular significance for certain groups, such as victims of disasters, the homeless, people in dangerous professions, relations of criminals, and victims of abuse.

Questions do not explore in depth the feelings of those who might be seriously mentally ill and perceive that their safety is threatened by "being persecuted by aliens", for example.

Questions focus on a person's own feeling of safety / lack of safety, security / insecurity in so far as these affect quality of life.

17. Home environment

This facet examines the principal place where a person lives (and, at a minimum, sleeps and keeps most of his / her possessions), and the way that this impacts on the person's life. The quality of the home would be assessed on the basis of being comfortable, as well as affording the person a safe place to reside.

Other areas which are included implicitly are: crowdedness; the amount of space available; cleanliness; opportunities for privacy; facilities available (such as electricity, toilet, running water); and the quality of the construction of the building (such as roof leaking and damp).

The quality of the immediate neighbourhood around the home is important for quality of life, and questions include reference to the immediate neighbourhood. Questions are phrased so as to include the usual word for "home" i.e. where the person usually lives with his/her family. However, questions are phrased to include people who do not live in one place with their family, such as refugees, or people living in institutions. It would not usually be possible to phrase questions to allow homeless people to answer meaningfully.

18. Financial resources

The facet explores the person's view of how his/her financial resources (and other exchangeable resources) and the extent to which these resources meet the needs for a healthy and comfortable life style. The focus is on what the person can afford or cannot afford which might affect quality of life.

The questions include a sense of satisfaction/dissatisfaction with those things that the person's income enables them to obtain. Questions include a sense of the dependence/independence provided by the person's financial resources (or exchangeable resources), and the feeling of having enough.

Assessment will occur regardless of the respondent's state of health or whether or not the person is employed. It is acknowledged that a person's perspective on financial resources as "enough", "meeting my needs", etc. is likely to vary greatly, and the questions are framed to allow this variation to be accommodated.

19. Health and social care: availability and quality

The facet examines the person's view of the health and social care in the near vicinity. "Near" is the time it takes to get help.

Questions include how the person views the availability of health and social services as well as the quality and completeness of care that he/she receives or expects to receive should these services be required. Questions include volunteer community support (religious charities, temples...) which either supplements or may be the only available health care system in the person's environment. Questions include how easy/difficult it is to reach local health and social services and to bring friends and relatives to these facilities.

The focus is on the person's view of the health and social services. Questions do not ask about aspects of health care which have little personal meaning or relevance to the person who will be answering the question.

20. Opportunities for acquiring new information and skills

This facet examines a person's opportunity and desire to learn new skills, acquire new knowledge, and feel in touch with what is going on. This might be through formal education programmes, or through adult education classes or through recreational activities, either in groups or alone (e.g. reading).

This facet includes being in touch and having news of what is going on, which for some people is broad (the "world news") and for others is more limited (vil-

lage gossip). Nevertheless, a feeling of being in touch with what is going on around them is important for many people and is included.

The focus is on a person's chances to fulfil a need for information and knowledge whether this refers to knowledge in an education sense, or to local, national or international news that has some relevance to the person's quality of life.

Questions are phrased in order to be able to capture these different aspects of acquiring new information and skills ranging from world news and local gossip to formal educational programmes and vocational training. It is assumed that questions will be interpreted by respondents in ways that are meaningful and relevant to their position in life.

21. Participation in and opportunities for recreation and leisure

This facet explores a person's ability, opportunities and inclination to participate in leisure, pastimes and relaxation.

The questions include all forms of pastimes, relaxation and recreation. This might range from seeing friends, to sports, to reading, to watching television or spending time with the family, to doing nothing.

Questions focus on three aspects: the person's capacity for, opportunities for and enjoyment of recreation and relaxation.

22. Physical environment (pollution/noise/traffic/climate)

This facet examines the person's view of his/her environment. This includes the noise, pollution, climate and general aesthetic of the environment and whether this serves to improve or adversely affect quality of life. In some cultures certain aspects of the environment may have a very particular bearing on quality of life, such as the central nature of the availability of water or air pollution.

This facet does not include *Home environment* or *Transport* as these are covered in separate facets.

23. Transport

This facet examines the person's view of how available or easy it is to find and use transport services to get around.

Questions include any mode of transport that might be available to the person (bicycle, car, bus...). The focus is on how the available transport allows the person to perform the necessary tasks of daily life as well as the freedom to perform chosen activities.

Questions do not enquire into the type of transport, nor do they explore means that are used to get around in the home itself. In addition the personal mobility of the individual is not included because this is covered elsewhere (*Mobility*).

DOMAIN VI - SPIRITUALITY/RELIGION/PERSONAL BELIEFS

24. Spirituality/religion/personal beliefs

This facet examines the person's personal beliefs and how these affect quality of life. This might be by helping the person cope with difficulties in his / her life, giving structure to experience, ascribing meaning to spiritual and personal questions, and more generally providing the person with a sense of well-being. This facet addresses people with differing religious beliefs (e.g. Buddhists, Christians, Hindus, Muslims), as well as people with personal and spiritual beliefs that do not fit within a particular religious orientation.

For many people religion, personal beliefs and spirituality are a source of comfort, well-being, security, meaning, sense of belonging, purpose and strength. However, some people feel that religion has a negative influence on their life. Questions are framed to allow this aspect of the facet to emerge.

Response scales

The questions that make up the WHOQOL-100 arose from a process designed to capture both the culture-specific interpretation of quality of life facets as well as language idiom. There was therefore, of necessity, some diversity in the nature and structure of the questions. Consequently, there was a trade-off between a minimum number of standardised question–response scale formats whilst still allowing an enquiry into difficult aspects of quality of life, and maintaining the unique face validity of the questions in the WHOQOL-100 in different cultures. To accommodate this there are four five-point response scales concerned with the intensity, capacity, frequency and evaluation of states or behaviours.

The **Intensity** response scale refers to the degree or extent to which a person experiences a state or situation e.g. the intensity of pain. Questions may also refer to the vigour or strength of a behaviour. The assumption is that the experience of a more intense state is associated with corresponding changes in quality of life. Example questions include: "Do you worry about any pain or discomfort?" and "Do you have any difficulties with sleeping?". One response scale is used to assess intensity. In English, the anchors on the scale are "Not at all" and "Extremely" or "An extreme amount".

The **Capacity** response scale refers to a capacity for a feeling, state or behaviour. The assumption is that a more complete capacity is associated with corresponding changes in quality of life. Example questions include: "Do you have enough energy for everyday life?" and "To what extent are you able to carry out your daily activities?". In English, the anchor points are "Not at all" and "Completely".

The **Frequency** response scale pairings refer to the number, frequency, commonness, or rate of a state or behaviour. The time frame is crucial to these questions, such that the frequency refers to its frequency in the specified time period. The assumption is that a greater number of occurrences of the state or behaviour is associated with corresponding changes in quality of life. Example questions are:

"How often do you have negative feelings, such as blue mood, despair, anxiety, depression?" and "How often do you suffer (physical) pain?" In English, the anchor points are "Never" and "Always".

The **Evaluation** response scale refers to the appraisal of a state, capacity or behaviour. The assumption is that a more positive evaluation is associated with a corresponding increase in the respondent's quality of life. Example questions are: "How satisfied are you with your capacity for work?" and "How satisfied are you with your personal relationships?" Several evaluation scales are employed. In English, the anchor points are "Very unhappy" – "Very happy"; "Very dissatisfied" – "Very satisfied"; and "Very poor" – "Very good". This response scale differs from the intensity, frequency and capacity scales in that it has as a neutral midpoint and the anchor points are not extreme points, to maximise full usage of the scale. In several languages (e.g. Croatian and Dutch) the distinction between the two question stems "How satisfied...?" and "How happy...?" does not translate and all of these questions and response scales therefore become "How satisfied...?"

Response scales have been derived for each of the WHOQOL-100's language versions according to a standardised methodology. Ensuring equivalence in response scales required a methodology that goes beyond translation of standardised English language scale descriptors. Although endpoints such as "Never" and "Always" are universal, shades of meaning between endpoints (e.g. "sometimes") are more ambiguous, difficult to translate, and subject to cultural variation in their interpretation. To ensure equivalence across WHOQOL field centres, a methodology was used which specified the anchor points for each of the four types of 5-point response scales (Evaluation, Intensity, Capacity and Frequency), and a scale metric which intermediate descriptors should fit. That is, descriptors for each of the response scales were derived to find words / terms falling at 25%, 50% and 75% points between the two anchors.

This methodology ensured first that response scales were not simply translated from a source language with all the problems associated with this process. Second, it secured a high degree of scalar equivalence between languages, which was supported by subsequent bilingual review. Third, it ensured equidistance between descriptors on the scales. The method whereby response scales were derived is described more fully elsewhere (Szabo, S., Orley, J. and Saxena, S. On behalf of the WHOQOL Group, 1997).

Annex X. Participants in the WHO Consultation on Methodologies for Research and Evaluation of Traditional Medicine

Hong Kong Special Administrative Region of China (Hong Kong SAR), 11–14 April 2000

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