GUIDELINES FOR CLINICAL STUDY *of* TRADITIONAL MEDICINES IN THE WHO AFRICAN REGION

WORLD HEALTH ORGANIZATION
Regional Office for Africa
Brazzaville

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[1] Short-term Professional, Regional Programme on HIV/AIDS
[2] Short-term Professional, Malaria Unit
[3] Short-term Professional, Traditional Medicine Programme (2000-2001)
[4] Short-term Professional, Traditional Medicine Programme (2002-2004)

FOREWORD

Traditional medicine is a comprehensive phrase which refers to several traditional medical systems, such as Chinese, African and Indian, and other forms of indigenous medical practices. In countries where the dominant health care system is based on modern Western medicine, or where traditional medicine has not been incorporated into the national health care system, traditional medicine is often termed as *complementary, alternative* or *non-conventional* medicine.

WHO defines traditional medicine as "The total combination of knowledge and practices, whether explicable or not, used in diagnosing, preventing or eliminating physical, mental or social diseases and which may rely exclusively on past experience and observation handed down from generation to generation, verbally or in writing" (WHO, 2001). In the WHO African Region, this traditional knowledge is transmitted by oral tradition while some specific recipes are disclosed only to family members for some specified diseases. Traditional medicine is known to have been used throughout the world ever since humankind has existed for the management of self-limiting to life-threatening illnesses. Today, about 80% of the population living in the African Region depends on traditional systems of medicine for their health care needs.

A survey conducted under the Roll Back Malaria programme has reported that in Ghana, Mali, Nigeria and Zambia, the first-line treatment for more than 60% of children with high fever is the use of herbal medicines at home. Some other surveys have shown that over three-quarters of AIDS patients in Africa, North America and Europe use traditional or complementary medicine for relief.

Worldwide, traditional or complementary medicine is used to treat chronic pain and to improve the quality of life of those suffering from incurable diseases. In India, for example, 65% of the population depends on traditional medicine to meet their health care needs. In other parts of Asia and Latin America, historical circumstances and cultural beliefs have sustained and promoted the use of traditional medicine by a majority of the populations. Certain complementary and alternative medical therapies are also popular among about 48% of the population in Australia, 50% in Canada, 42% in the United States of America, 40% in Belgium and 75% in France.

Despite the worldwide use of traditional medicine, evidence of the efficacy of treatments is generally lacking, raising issues about safety, rational use and cost-effectiveness. A considerable amount of research and clinical evaluation of the safety and efficacy of traditional medicine is, therefore, urgently needed, especially for life-threatening conditions such as malaria, HIV/AIDS, hypertension and asthma, for which potential traditional medical treatments do exist.

The WHO Regional Committee for Africa, in 1999, requested the Regional Office to develop a comprehensive regional strategy on traditional medicine. By its resolution AFR/RC49/R5 on *Essential drugs in the WHO African Region: Situation and trend analysis,* the Committee requested the Regional Director to support countries in conducting research on medicinal plants and promoting their use in health care delivery systems. A regional document, *Promoting the role of traditional medicine in health systems: A strategy for the African Region* was adopted by the Regional Committee in 2000.

Resolution AFR/RC50/R3 requests Member countries to produce evidence of safety, efficacy and quality of traditional medicines and to strengthen research institutions to conduct relevant research and disseminate results. The Regional Office thus selected five priority diseases: HIV/AIDS, malaria, sickle-cell disorder, diabetes and hypertension.

A number of countries in the African Region are at different stages of doing research and developing and manufacturing traditional medicines for treating common ailments and the five priority diseases. Some of these traditional medicines have been registered and included in national essential drugs lists. In a health centre in Ouagadougou, Burkina Faso, over 1200 people living with HIV/AIDS were recruited for study. Researchers have confirmed improvement as evidenced by a marked increase of CD4 values in patients, all of whom are being treated exclusively with traditional medicines. Similarly, laboratory investigations showed a significant decrease in the viral load count of the patients. In addition, improvements have been noted in the quality of life, weight gain and clinical condition of the patients. WHO is supporting the laboratory investigations of the study. Similar results have been observed in Côte d'Ivoire, Nigeria, South Africa and Zimbabwe. It is important to increase access to safe, effective and quality traditional medicines for HIV/AIDS patients and those affected by other priority diseases.

These guidelines have been developed to assist countries in the African Region to conduct systematic scientific and clinical research to produce evidence on the safety, efficacy and quality of traditional medicines. It is expected that Member countries would provide feedback to WHO so that they can be improved further. I am confident that this publication will go a long way in supporting researchers to produce evidence on the safety, efficacy and quality of herbal medicines.

It is my hope that the Region will soon produce enough therapies from our rich heritage of medicinal plants to benefit our suffering populations in order to reduce morbidity and mortality associated with HIV/AIDS, malaria, sickle-cell disorder, diabetes and hypertension. As I have often emphasized, African traditional medicine is our own heritage; if we do not develop it ourselves, nobody else will.

Dr Ebrahim Malick Samba
Regional Director

World Health Organization
Regional Office for Africa

In addition to the two model research protocols developed at a meeting in Madagascar, the Traditional Medicine Programme in collaboration with the WHO Regional Expert Committee on Traditional Medicine developed protocols for the clinical evaluation of traditional medicines used for the management of sickle-cell disorder, diabetes and hypertension. The five research protocols on HIV/AIDS, malaria, sickle-cell disorder, diabetes and hypertension were combined into one document: a model for clinical observational study of traditional medicines. This model was reviewed at the regional workshop on traditional medicines research and development, intellectual property rights and biodiversity, held in Johannesburg, South Africa from 24 to 27 November 2003. The participants agreed that countries need a model generic research protocol due to the fact that the general principles for evaluation of traditional medicines are the same irrespective of the target disease. However, it was agreed that any peculiarities inherent in the evaluation of traditional medicines for specific diseases could be included in the annexes.

These *Guidelines for Clinical Study of Traditional Medicines in the WHO African Region,* which are based on the five research protocols mentioned above, have been developed in response to the decision taken at the Johannesburg meeting. These guidelines provide a generic document which can be adopted and adapted appropriately by biomedical researchers in the WHO African Region for clinical study of traditional medicines. One of the key elements hindering the process of registration of traditional medicines and their subsequent rational use is the lack of valid clinical data on their safety and efficacy. It is hoped that this document would provide the template for developing specific protocols for evaluating traditional medicines, which will promote the generation of valid clinical data on traditional medicines. Although the effectiveness of traditional medicines has been reported based on long-term experiential use, clinical studies play a significant role in proving the effectiveness of traditional medicines in a scientific manner. Only clinical study can guarantee the integration of traditional medicine into mainstream health care and ensure its expanded use. Clinical study also provides valid data for further development of potential innovative new medicines from traditional medical recipes and medicinal plants.

Purpose of the guidelines

The purpose of this document is to promote research on traditional medicine and facilitate the evaluation of the quality, safety and efficacy of traditional medicines using acceptable clinical methodology. This document will assist Member States to standardize the methodology for clinical evaluation of traditional medicines used for the management of HIV/AIDS, malaria, sickle-cell disorder, diabetes and hypertension. In addition, there is need to protect the innocent public from possible harmful effects of African traditional medicines routinely used for treating various diseases or without any beneficial effects at all. Such a situation may consequently accelerate disease progression. On the other hand, there is the possibility of dealing with some pharmacologically beneficial traditional medicines which require proper assessment to facilitate their public utilization. The model protocol is for institutions conducting research in the WHO African Region. It contains information for clinical evaluation of traditional medicines following the principles of good clinical practice, the Helsinki Declaration and the Basic Principles in Clinical Research (see annexes). Country experiences in Africa have greatly contributed to the development of these guidelines. Relevant materials have been included as annexes. It is therefore, a reference document that government regulatory agencies and research institutions can use in the context of their national health research policies.

Target audience of the guidelines

This document is intended for use by health institutions conducting research, including WHO collaborating centres, agencies and companies involved in the development of traditional medicine in the African Region, traditional health practitioners, pharmacologists, pharmacists, experts and professionals.

Structure of the document

This document is divided into three parts. Part I outlines procedures for clinical study for evaluating the safety and efficacy of traditional medicines used for the treatment of priority diseases. Part II gives some additional information for developing protocols for evaluating safety and efficacy of traditional medicines used for the treatment of HIV/AIDS, malaria, sickle-cell anaemia, diabetes and hypertension. This section details the peculiarities inherent in the evaluation of traditional medicines for these specific diseases, and the information should be used in addition to the procedures provided for in the generic guidelines. The last part contains information materials related to the proper conduct of clinical trials. These materials are available as published and unpublished WHO documents, but due to the difficulty encountered by biomedical researchers in sub-Saharan African countries regarding access to available information, a few of such valuable materials are included in this document for easy access.

2. BACKGROUND INFORMATION

2.1 General background

In designing clinical protocols, it is necessary to consider both administrative and technical issues which will facilitate management of the clinical study. Administrative issues include the following:

(a) Protocol identification number

(b) Name and address of the monitor

(c) Name and title of the person authorized to sign the protocol and protocol amendments for the sponsor

(d) Name and address of the sponsor

(e) Name, title, address and telephone number of the sponsor's medical expert for the trial

(f) Name and title of the investigator(s) responsible for conducting the trial and the address and telephone number(s) of the trial sites

(g) Names and addresses of the clinical laboratories, hospitals and other medical institutions involved in the trial.

Technical issues include the following:

(a) Name and description of the investigational product
(b) A summary of anecdotal and ethnomedical evidence regarding the safety and efficacy of the product, if available
(c) A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial, if available
(d) A summary of the known and potential risks and benefits, if any, to human subjects
(e) A description of and justification for the route of administration, dosage, dosage regimen and duration of treatment
(f) A statement that the trial will be conducted in compliance with the WHO *Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products* and the applicable national regulatory requirements
(g) A description of the population to be studied
(h) References to literature and data that are relevant to the trial and that provide background for the trial.

2.2 Pre-clinical data on traditional medicines

The minimum requirements for product development include pre-clinical research data on safety and efficacy as well as clinical data. With regard to traditional medicines with long history of human use, acceptable ethnomedical evidence on safety and efficacy may serve as important pre-clinical data. The focus here is to provide credible, verifiable and generally acceptable evidence that will enable the product to be evaluated quickly but properly.

2.3 Ethnomedical evidence

Ethnomedical evidence is the summation of information adduced, based on a retrospective study, to provide the scientific basis for the practice of an African traditional medicine or the use of a herbal remedy. Unlike some Asian countries such as China, India and Japan, no written documents are available for many of the African traditional medicines, and even in the case of those that have such records, they have been produced very recently. It is, therefore, imperative that any ethnomedical evidence collected must be verifiable according to three essential criteria for any treatment or therapeutic agent:

(a) Identity: The nature, source, history and description of the practice or the remedy;
(b) Safety: The degree of safety of the practice or remedy and any traditional methods of ensuring reliability and safety;

(c) *Efficacy:* The traditional history of the efficacious use of the traditional treatment for the disease condition.

In adducing ethnomedical evidence for a practice or a remedy, the goal must be to show, through the use of scientific evidence, that the treatment has been applied as an African traditional medicine.

2.4 Clinical study

It should be emphasized that there are standard minimum requirements for designing clinical research protocols, which are modified depending on the targeted disease and in accordance with prevailing national regulations. This situation notwithstanding, expertise in clinical research in Africa is weak. Thus, this document provides a template, which can be adapted appropriately by biomedical researchers in Africa. The document only covers key elements for a standard clinical protocol. Some peculiarities for evaluating new medicines against some priority diseases (e.g. HIV/AIDS, malaria, sickle-cell disorder, diabetes and hypertension) are indicated in Part II of this document.

2.5 General approach to the safety and efficacy of traditional medicines

(a) Collect information based on traditional use.

(b) Scientifically ascertain the safety of traditional medicines which generates vital data for dosage specifications.

(c) Repeat the necessary laboratory investigations to obtain sufficient data for clinical trial protocol.

3. TRIAL OBJECTIVES AND PURPOSE

The general objective is to evaluate the safety and efficacy of African traditional medicines (ATMs). The specific objectives are to conduct preliminary safety assessments of ATMs for specified diseases and to conduct preliminary efficacy assessment of ATMs for specified diseases.

The purpose of the study is to generate clinical and laboratory data which will guide the decision regarding the registration and rational use of ATMs.

4. GENERAL PROCEDURE

4.1 Research team

The research team should be recruited to include some or all of the following experts and professionals: the traditional health practitioner who gives the initial recipe, a clinician who is a consultant in the disease chosen for the study, a laboratory technician, a pharmacologist or a pharmacist, a nurse, a botanist, a statistician and a legal practitioner.

The clinician is usually the team leader. The team should meet before the start of the study to discuss and agree on the specific modalities, assign responsibilities and draw up an acceptable work plan. All members of the research team will be given an orientation on the project, using predetermined standard procedures. The team leader shall serve as the principal investigator, who will be vested with all professional and financial responsibilities of the study.

4.2 Schedule of visits for clinical and biological evaluation

The volunteers are expected to visit the health facility for initial baseline clinical assessment, then monthly till the end of the study. Samples will be collected from the study participants at the baseline and regularly for biological evaluation. The frequency of collecting biological samples from the trial subjects will depend on the target disease. Appropriate laboratory investigation forms should be designed which should indicate the types of tests to be carried out and their timing. The contents of such forms will vary according to the target disease.

4.3 Support for the subjects

A subsidy for food and travel expenses of the patients, the cost of treatment at the health facility and allowances for members of the research team should be considered as part of the budget for the study. It is anticipated that such incentives would encourage the volunteers to attend the clinics regularly as per the schedule of visits.

5. TRIAL DESIGN

5.1 End-points of the trial

Primary end-points

(a) Development of or delay in the development or resolution of symptoms associated with the disease or a significant reduction/complete clearance of parasites/organisms implicated in the etiology of the disease or death.

(b) Degree of quality of life (see details in Karnofsky Performance Scale, Annex 3).

Secondary end-points

(a) Significant changes in the biological marker of the disease (e.g. haematological/ immunological parameters).

(b) Development of drug-related toxicities sufficiently severe to warrant dose modification, interruption or permanent discontinuation.

5.2 *Type of design*

Different designs are used depending on the expected outcome of the study and the stage of development of the medicines vis-à-vis their clinical use. Examples of study designs include single dose, black box, ethnographic, observational studies which can be either controlled or uncontrolled and/or randomized (see Clinical Research in Annex 5 for further details). This study design will vary in accordance with the stage of development of the ATM.

5.3 *Phases of clinical trials*

Clinical trials are divided into four phases. Phase I involves the assessment of the safety of the medicine in healthy volunteers (about 20), while phase II seeks to assess the efficacy and relative safety of the medicine in a few subjects (numbering 100 to 200) at one study site. Phase III usually involves 200 to 1000 subjects utilizing multiple study sites and aims at generating data on the safety and efficacy of the new medicine. Phase IV is post-marketing surveillance, which targets the safety and efficacy of the new medicine in the general population after it has been registered and been in public use. Such phase IV studies may also reveal a new medical use for the medicine. It should be noted that prior to embarking on controlled clinical trials, pharmacokinetic and dose studies should be conducted at the phase II level which will assist in making a decision regarding the dosage and frequency of administration for either controlled phase II or phase III.

5.4 *Choice of disease for study*

The choice of disease for study should be guided by national epidemiological data on the incidence and severity of the disease. The issues of the availability, affordability, effectiveness, safety and accessibility of conventional medicines for the chosen disease should also be adequately evaluated. The WHO Regional Office for Africa has identified five priority diseases (malaria, HIV/AIDS including TB, sickle-cell disorder, hypertension and diabetes) to be initially targeted for research in and development of African traditional medicines.

5.5 *Selection of traditional health practitioner*

The traditional health practitioner (THP) who is considered for inclusion in the study should be recognized in his community for successfully managing the specified disease, hence qualified to practise traditional medicine. If possible, the practitioner should be a well-known member of an existing national association of THPs, if it exists. Furthermore, anecdotal evidence regarding the safety and efficacy of the traditional medicine used by the chosen practitioner would be useful.

5.6 *African traditional medicines to be used for study*

The choice of the traditional medicine for study should be guided by the ethno-botanical information and an overview of existing literature. Furthermore, there should be reliable information that a particular medicine has been traditionally used with anecdotal evidence of safety and efficacy. In such a case, there should be no need for laboratory studies before initial observational studies, but these should be done after the completion of the study or concurrently with the case-study depending on the information available on the particular traditional medicine. The observations of the patients who choose to take these remedies as well as clinical data collected by the research team during the study, will determine whether further laboratory and clinical studies are necessary.

The following information about the medicine shall be recorded:

(a) Name of product
(b) Information on the traditional use of the product (e.g. fever due to malaria, diabetes and for treating people living with HIV/AIDS).

It is important at this initial stage to define who owns the intellectual property rights of the traditional medicine, i.e. whether this belongs to an individual health practitioner, a group of health practitioners or a whole community or ethnic group. Steps should be taken to protect their intellectual property rights with a view to drawing up a benefit-sharing agreement should the research proceed any further.

In order to preserve intellectual property rights, all the above-mentioned information need not always be published; however, it should be recorded and retained in at least two copies by the principal investigator and the informant in a safe place for future reference, should further research be necessary.

5.7 *Study sites*

The sites required will vary according to the type of the clinical study. For example, in the case of a clinical observational study, the primary site would be the traditional health practitioner's facility where the subjects receive the treatment. Collection of biological samples may also be done at the THP's facility, subject to its adequacy for this kind of work. Alternatively, collection of biological samples can be carried out at the secondary site, which is the conventional health facility where laboratory investigations and monitoring of patients can be done.

5.8 *Dose schedule and route of administration*

The dose of any specific ATM will be determined by the dose used by the THP, the toxicity data, the pharmacokinetic data and the results of dose escalation studies. In Africa, liquid and powdered preparations are the most frequently-used formulations for oral administration. Moreover, ATMs can also be applied topically as well as inhaled.

5.9 Treatment duration

A study period of 3 to 12 months is regarded as adequate to generate preliminary observational clinical data. The actual period will, however, be determined by the nature of the disease. For example, three and 12 months are the recommended treatment periods for clinical observational studies of traditional medicines used for the management of malaria and HIV/AIDS, respectively, subject to national regulations.

5.10 Discontinuation of treatment

Any participant is free to discontinue the trial at any time during the study. On the other hand, the principle investigator may withdraw a participant from the study due to anaphylaxis and allergic symptoms of dyspnoea or wheezing, itching or erythema. Furthermore, a participant may be withdrawn if he/she fails to respond to the treatment with the traditional medicine and his/her condition is deteriorating.

5.11 Treatment of adverse effects

It should be emphasized that the principal investigator has the professional responsibility with regard to the management of adverse effects. It is recommended that appropriate interventions should take cognizance of the national standard treatment guidelines and associated complications.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

The study participants are selected by the research team based on the selection criteria for the study. The approval for study and ethical issues as indicated in Section 13 should be strictly adhered to.

A categorical statement on the diagnostic criteria to be used should be stated to allow for uniformity and reproducibility. The criteria to be used for subject inclusion and exclusion should be properly described and should be as realistic as possible.

Details regarding how and when to withdraw subjects as well as how to treat the data from such subjects should be clearly indicated. Furthermore, it should be indicated if the withdrawn subjects are to be replaced and the modality for replacement.

7. TREATMENT OF SUBJECTS

The dosage and route of administration are indicated above (Section 5). The follow-up periods should be clearly indicated and explained to the subjects. As a general rule, conventional medicines should not be taken concurrently with traditional medicines in order to avoid possible harmful drug interactions. However, the principal investigator may consider administration of certain conventional medicines depending on the disease(s) being treated and possible subsequent complications if untreated. The procedures for monitoring subject compliance with medication should be developed prior to the commencement of the trial and enforced during the trial.

PART II

DEVELOPMENT OF PROTOCOLS

This part deals with some specific aspects of protocol design relating to evaluation of traditional medicines against some priority diseases. It is important that Part II of this document be used together with Part I in designing any protocol for the evaluation of traditional medicines against any of the priority diseases discussed below.

19. HIV/AIDS

The general objective is to evaluate the efficacy and safety of traditional medicines used for the treatment of HIV/AIDS. Specific objectives are:

(a) To confirm the biological and clinical diagnosis;
(b) To determine the clinical efficacy of the herbal product;
(c) To document any side-effects related to the use of the product;
(d) To determine changes in the HIV-related symptoms;
(e) To determine changes in CD4 and CD8 counts;
(f) To provide clinical, social and psychological support for people living with HIV/AIDS;
(g) To determine changes in the viral load during therapy with the product.

DATA

Relevant data on pre-clinical study, especially on safety (toxicity studies), as well as retrospective study regarding ethnomedical evidence on both safety and clinical efficacy, should be included. Data from such studies should indicate promising potential usefulness of the traditional medicine to justify the conduct of a pilot clinical trial.

METHODOLOGY

Criteria for patient selection

Inclusion criteria

(a) Male or female age >15 years.
(b) HIV infection documented by licensed ELISA confirmed by:
(c) Western Blot or

10. Any other treatment that may be given or permitted concomitantly.

11. Clinical and laboratory tests, pharmacokinetic analysis, etc., that are to be carried out.

12. Description of how responses are recorded (description and evaluation of methods and frequency of measurement), follow-up procedures and measures to determine the extent of compliance with the treatment among trial subjects.

13. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.

14. Methods for recording and reporting adverse events or reactions, and provisions for dealing with complications.

15. Procedures for the maintenance of subject identification code lists, treatment records, lists for the randomization of subjects and/or case-report forms (CRFs). Records should permit identification of individual patients or participants as well as auditing and reconstruction of data.

16. Information about how the trial code is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency.

17. Measures to be implemented to ensure the safe handling and storage of investigational and comparator products, if used, and to promote and determine the extent of compliance with the prescribed treatment and other instructions.

18. Description of methodology to be used to evaluate the results, (including statistical methods) and to report on patients or participants withdrawn from the trial.

19. Time schedule for completion of the trial.

20. Information to be presented to the trial subjects, including how they will be informed about the trial, and how and when their consent will be obtained.

21. Instructions for staff involved in the trial, including how they are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.

22. Ethical considerations and measures relating to the trial.

23. Medical care to be provided after the trial, modalities of post-trial treatment.

24. When the protocol serves as a contract, statements regarding financing, insurance, liability, delegation or distribution of responsibilities, and publication policy.

25. List of literature referred to in the protocol.

PART II

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(g) To determine changes in the viral load during therapy with the product.

DATA

Relevant data on pre-clinical study, especially on safety (toxicity studies), as well as retrospective study regarding ethnomedical evidence on both safety and clinical efficacy, should be included. Data from such studies should indicate promising potential usefulness of the traditional medicine to justify the conduct of a pilot clinical trial.

METHODOLOGY

Criteria for patient selection

Inclusion criteria

(a) Male or female age >15 years.
(b) HIV infection documented by licensed ELISA confirmed by:
(c) Western Blot or

i) positive HIV blood culture, or
ii) positive HIV serum antigen, or
iii) second antibody test positive by a method other than ELISA.

(d) CD4+cell count >100/mm^3 within 2 weeks prior to entry.
(e) Ability to provide written informed consent to participate in the trial.
(f) Ability to comply with the protocol.

EXCLUSION CRITERIA

(a) Previous treatment with any antiretroviral medication.
(b) Life threatening opportunistic disease/infection.
(c) A history of lymphoma.
(d) Patient is a pregnant woman who intends to carry the pregnancy to term, or is breastfeeding, or is of childbearing potential not employing adequate birth control.
(e) Peripheral neuropathy (moderate to severe).
(f) Treatment with radiation therapy or cytotoxic chemotherapeutic agents within four weeks prior to entry, or an anticipated need for such treatment during the protocol-led study period.
(g) Treatment with any immunomodulating agents within four weeks prior to entry.
(h) Use of any investigational drug <30 days prior to the start of the study.
(i) Significant cardiac dysfunction requiring maintenance therapy with cardiac glycosides, antiarrhythmics or vasodilators.
(j) Active alcohol or drug abuse to such an extent that, in the investigator's opinion, it will prevent compliance with the dosing schedule and evaluations.
(k) Severe kidney and/or and liver dysfunction.

SCHEDULE OF VISITS FOR CLINICAL AND BIOLOGICAL EVALUATION

The volunteers are expected to visit the hospital for clinical and psychosocial assessment, once a week if possible, during the first month of therapy. Then, fortnightly during the second month, and thereafter, once a month till the end of the study. Follow-up visits should continue after the study on a monthly basis for two years in the first instance.

Samples will be collected from the study participants every three months for biological evaluation and every 4–6 months for viral load assessment.

END-POINTS OF THE TRIAL

Primary end-points

(a) Development of or delay in the development or resolution of AIDS-defining diseases or death

(b) Degree of quality of life (Karnofsky performance score).

Secondary end-points

(a) Degree and duration of reduction of HIV load

(b) Changes in CD4/CD8 ratio from baseline

(c) Development of drug-related toxicities sufficiently severe to warrant dose modification, interruption or permanent discontinuation.

20. MALARIA

The general objective of these guidelines is to standardize the methodology for documenting the ethnomedical evidence and clinical evaluation of antimalarial traditional medicine in order to improve the quality and comparability of clinical trials in this field. The specific objectives are to determine the efficacy of traditional herbal medicines when given orally in the treatment of uncomplicated malaria, and to assess the safety of traditional medicines when used for the treatment of uncomplicated malaria.

DATA

Relevant data on pre-clinical study, especially on safety (toxicity studies), as well as retrospective study regarding ethnomedical evidence on both safety and clinical efficacy, should be included. Data from such studies should indicate promising potential usefulness of the traditional medicine to justify the conduct of a pilot clinical trial.

METHODOLOGY

Criteria for patient selection

Inclusion criteria

(a) Age 18 to 45 years

(b) Uncomplicated malaria, i.e. absence of danger signs

- Parasitaemia of >1000 per mm^3 of a defined species
- No history of ingestion of known antimalarials within past seven days (investigators may choose not to exclude patients having taken chloroquine, depending on the epidemiological situation in the study area)
- Informed consent of patient or parent/guardian to take part in the study (see Annex 1)
- Patient able and willing to return for follow up.

Exclusion criteria

(a) Complicated malaria, i.e. danger signs—evidence of cerebral involvement (meningitis or encephalitis), hypertension, vomiting, dehydration, renal involvement

(b) Other causes of febrile illness

(c) Pregnant women (pregnancy test should be done if status uncertain)

(d) Haemoglobin less than 5 grams per deciliter (dl)

(e) Positive urine test for antimalarials or history of ingestion of antimalarials within past seven days (optional for chloroquine, see above)

(f) Patients with medical conditions necessitating the concurrent use of other medications

(g) Patients with other major underlying medical conditions, e.g. cardiac or renal disease.

Non-admissible patients, i.e. those with any of the exclusion criteria will be offered standard alternative treatment.

Sample size

This should be calculated to be able to detect a difference of 20% or more between the herbal preparation and the standard local first-line antimalarial preparation, with confidence of 95% and power of 90%. A statistician should be involved in the process at an early stage.

Screening phase

Clinical assessment before commencing treatment. For further details, see sample of a Summary Case-Record Form at Annex 6.

Serum chemistries

These will include liver function tests (bilirubin, transaminases, gammaglutamine transaminases (ã-GT), alkaline phosphatase, albumin and total protein), electrolytes sodium, potassium (Na^+, K^+), urea and creatinine, and random blood glucose (as many of these as possible).

Haematology

A full haemogram and total differential white cell count will be done. A thick and thin blood smear will also be made to determine parasitaemia. A reticulocyte count should be done.

In vitro sensitivity tests (optional).

Treatment phase

This may consist of outpatient observation up to day 28. If facilities are available, patients may be admitted for one day longer than the duration of the treatment to observe for idiosyncratic adverse effects, and to monitor the response to treatment.

RANDOMIZATION

Patients will be randomized to receive either the herbal preparation or the control drug. A simple randomization procedure may be used. Alternatively, a pseudo-randomization procedure may be adopted by using balanced block randomization where a balance will be achieved for every sixth or patient. This method may be adopted due to time trends that may develop over the 28 days of follow up. The patients would be randomized into any of the ten blocks of six patients each on arrival at the hospital or the recruiting centre. A block will be selected by the use of a table of random numbers. It will be a single blind trial where the clinician will not know the drug the patient is taking.

Drug administration

Traditional herbal remedy to be tested

The following are the prerequisites for a randomized clinical trial:

(a) A standard preparation administered orally according to a regimen defined by ethnomedical observations

(b) Sustainable supply of the medicinal plant raw material, and conservation measures to protect it

(c) Laboratory data to demonstrate lack of toxicity: cytotoxicity, teratogenicity, acute, sub-acute and sub-chronic toxicity (2-4 weeks), LD50—mouse and guinea-pig—or maximum tolerated dose.

This list is not mandatory. As many of these tests as possible should be done according to resources available and as per the national drug registration legislation. Clinical data (good data from a cohort or phase I study) to demonstrate safety and tolerability in humans may serve as an alternative to the above.

The following characteristics are desirable but not essential:

(a) Laboratory evidence of efficacy as an antimalarial

(b) No local use as a treatment (because if people are taking the plant anyway, this will interfere with the trial, although this prerequisite may be difficult to ascertain. Therefore, patients should be encouraged to state whether or not they are on local treatment).

Control treatment

The control group will receive the standard locally-used first-line treatment for uncomplicated malaria.

Parasitaemia

Thick and thin blood smears will be done on days 0, 3, 7 and thereafter on days 14 and 28, and any other day if the patient develops signs of severe malaria or revisits with symptoms.

Serum chemistries

These will be repeated on days 3, 7, 14 and 28, and will include the same tests as above.

Haematology

Full blood count will be repeated on days 3, 7, 14 and 28.

Physical examination and vital signs

The patients will have a physical examination done at the time of enrolment and again on days 7, 14, 28 and on any other revisits. The temperature will be taken on days 0-3, 7, 14 and 28. The pulse rate, blood pressure and respiration rate can be taken every six hours if the patient is admitted to hospital during the treatment phase.

Electrocardiogram (ECG) examinations

ECG examinations will be carried out at the time of admission, and then on days 3, 7, 14 and 28.

Side-effects

The side-effects will be documented as they appear (see Annexes 7 and 8).

Assessment of efficacy

Primary outcome measures

(a) Early treatment failure (modified), late treatment failure, adequate clinical response (see definitions in case reports)

(b) Proportion of patients with mild, moderate and severe side-effects (see below)

(c) Withdrawal from study.

Secondary outcome measures (optional)

(a) Full response

(b) Parasite clearance at days 7, 14 and 21

(c) Fever clearance at days 3 and 7

(d) Partial response

(e) Patients will be considered to have a partial response if they show a reduction in parasitaemia and no clearance by day 7. Reappearance of parasitaemia by day 14.

(f) No response

(g) Patients will be considered not to have responded if their condition remains the same or gets worse as determined by:

- Increase in parasitaemia from the baseline
- Increase in temperature or persistence of fever after 48 hours

- Onset of symptoms and signs indicative of complicated malaria (encephalitis, meningismus, drop in .... haemoglobin, vomiting, dehydration, hypotension and renal failure).

Assessment of safety

Safety will be assessed by comparing the baseline symptoms, vital/physical signs, haematology, serum biochemistry and ECG with those recorded at subsequent follow-up visits.

The following definitions of side-effects will be used (Annexes 3 and 9):

(a) Mild, tolerable, patient up and about

(b) Moderate, causes discomfort, but up and about

(c) Severe interferences with patient's activities.

Discontinuation from study

Patients who show early or late treatment failure will be offered alternative treatment.
Subjects will be withdrawn from the study if they have a moderate or severe adverse reaction. The reaction should be recorded (Annex 8), and the treatment should be stopped or changed as appropriate.
Subjects will be allowed to withdraw from the study for whatever reason, without compromising their continued care.

21. SICKLE-CELL DISORDER

The general objective is to evaluate the efficacy and safety of a traditional medicine for the management of sickle-cell anaemia. Specific objectives are to determine the clinical efficacy of a traditional medicinal product and to determine the side-effects associated with the use of a product.

DATA

Relevant data on pre-clinical study, especially on safety (toxicity studies), as well as retrospective study regarding ethnomedical evidence on both safety and clinical efficacy, should be included. Data from such studies should indicate promising potential usefulness of the traditional medicine to justify the conduct of a pilot clinical trial.

METHODOLOGY

Criteria for patient selection

Inclusion criteria

This should describe the characteristics of the subjects to be recruited for the study. Examples include male or female, age, etc. Additional characteristics should include:

(a) age: above 15 years
(b) sickle-cell disorder confirmed by electrophoresis of the haemoglobin
(c) history of at least three major sickle-cell crises in the previous year
(d) patient is capable of complying with the protocol
(e) memorandum of consent signed by the patient (adult) or by the legal guardian (in case of a minor).

Exclusion criteria

Exclusion criteria should describe the characteristics of the subjects that do not qualify to be included in the study. These include:

(a) patients on other medication for sickle-cell anaemia
(b) pregnant or breastfeeding women
(c) presence of serious heart anomalies
(d) presence of serious renal or hepatic anomalies.

Biological and clinical follow-up

Clinical check-up

(a) Anthropometric parameters: age, sex, weight, height, perimeter of skull, brachial perimeter, temperature
(b) Medical history
(c) Full clinical examination
(d) Immunization status

Biological check-up

(a) Electrophoresis of the haemoglobin (also parents and siblings)
(b) Blood level of fetal haemoglobin (where appropriate and possible)
(c) Blood group + Rh
(d) Complete haemogram
(e) Rates of reticulocytes
(f) Protidogram/C Protein reagent
(g) Bilirubin
(h) Ferritin
(i) Transferrin
(j) Hepatic and renal test

Frequency of biological and clinical follow-up

Study subjects should report to the medical centre for the initial check-up and then once a month for the clinical and biological examinations until the end of the follow-up.

Clinical evaluation criteria

A description should be given of the criteria to be used in the evaluation of the clinical effects of the product. Specific efficacy indicators should be established before the commencement of the study. Examples of such indicators include: change in (a) frequency of crisis; (b) severity of crisis; (c) anaemia; and (d) hospitalization. The indicators should be quantified and the effectiveness of the drug should also be graded.

Assessment of efficacy and safety

On the basis of the efficacy criteria established and their quantification and grading as defined under "Clinical evaluation criteria" above, as well as the safety profile based on the documented side-effects and their quantification, an assessment of the efficacy and safety of the product should be undertaken.

22. DIABETES

The general objective is to assess the efficacy and safety of the traditional medicine used for the management of diabetes. Specific objectives are to determine the clinical efficacy of a product, to assess the safety profile of the traditional medicine and to determine the side-effects associated with the use of a product.

DATA

Relevant data on pre-clinical study, especially on safety (toxicity studies), as well as retrospective study regarding ethnomedical evidence on both safety and clinical efficacy, should be included. Data from such studies should indicate promising potential usefulness of the traditional medicine to justify the conduct of a pilot clinical trial.

METHODOLOGY

Criteria for patient selection

Inclusion criteria

(a) Patients suffering from type II diabetes

(b) Levels of glycaemia on empty stomach (FBG) above 140 mg/dl (WHO, 1985)

(c) Men and women

(d) At least aged 30 years (30 to 60 years).

The ideal situation will be to have patients who have not yet been treated with any medication.

Exclusion criteria

(a) Pregnant or nursing mothers
(b) Type I diabetic patients
(c) Kidney failure, hepatic failure, heart failure
(d) Patients in poor health
(e) Patients on treatments that can have an impact on the glucidic and lipidic metabolism such as corticosteroids, oral contraceptives, drugs stimulating the thyroid and/or lowering lipidic rate
(f) Patients too weak to be included
(g) Hypertension (diastolic pressure above 90 mmHg)
(h) Sickle-cell anaemia or other genetic diseases
(i) Alcoholism or other associated defects.

Selection phase

Clinical test

All patients included in the study will undergo a full clinical test. The medical history of each patient including (a) demographic data, and (b) physical signs will be taken into consideration and will feature in the observation notebook.

Initial electrocardiograms (ECG) will be performed on each patient before they are included in the test.

Fasting blood sugar level test

The blood taken on day 0 (before treatment) will be used to determine the level of glycaemia on empty stomach. Plasmatic hyperglycaemia will be the main diagnostic criteria for inclusion in the study.

Biochemical tests

Tests on HbA1c glycocelia haemoglobin, lipidic fractions, uric acid, ALAT-ASAT and PAL (hepatic status : Alanine amino-transferasis, Aspartic amino-transferasis and alkaline phosphatasis), á-amylasis, creatinine, (Na+/K+) electrolytes, full and direct bilirubin, full proteins, albumin (and globulin) and G6PD status will also be performed.

Blood test

A complete haemogram will be done for each patient.

Urine test

Instantly collected urine will be tested with a reagent strip to determine the possible presence of proteins, glucose, acetone bodies or blood.

Follow-up tests

The clinical evaluation, including physical examination of subjects will be carried out on each patient during the follow-up visits.

Pre-clinical control tests will also be carried out.

Evaluation of drug safety

Considering side-effects, all events occurring during the study or during a reasonable period of time, whether they are considered as being associated with the administration of the preparation or not, will be evaluated by comparing them to the basic symptoms, the vital/physical signs, the para-clinical parameters (haematology, biochemistry, ECG and urine tests) with those carried out during subsequent follow-up tests. The judgment will be based on the Karnofsky scale and the WHO toxicity classification (Annexes 3 and 9). Patients who continue to present a low therapeutic balance (plasmatic glycaemia on empty stomach of above 7.7 mmol/L) one month after increasing the dosage of the plant extract will receive treatment with conventional drugs (glibenclamide or metformine).

Schedule of visits for clinical and biological evaluation

The volunteers are expected to visit the health facility for an initial baseline clinical assessment, then monthly till the end of the study. Samples will be collected from the study participants at baseline and every month for biological evaluation. Appropriate laboratory investigation forms should be designed, which will indicate the tests to be carried out and when the tests are to be conducted. The schedule of visits for clinical and biological evaluation may deviate from what has been suggested, depending on the national regulations for such matters and the realities on the ground.

Evaluation of the efficacy of treatment

With the prescribed dose of the drug, the expected results are as follows:

Efficacy: Good therapeutic balance; HbA1c about 6.5%, normal value of 4.5%–6.2%; plasmatic glycaemia on empty stomach from 4.4–6.7 mml/L on 3 consecutive occasions
Partial efficacy: Acceptable therapeutic balance; 6.6% < HbA1c < 7%; plasmatic glycaemia on empty stomach from 6.7–7.7 mmol/L on 3 consecutive occasions
Inefficacy: Poor therapeutic balance; HbA1c > 7%; plasmatic glycaemia on empty stomach above 7.7 mmol/L on 3 consecutive occasions.

Note that plasmatic glycaemia is a diagnostic criterion for diabetes. HbA1c is a therapeutic balance criterion.

WITHDRAWAL FROM STUDY

Withdrawal from the study may be at the request of the patient (withdrawal with patient's consent). There may be inefficacy: Plasmatic glycaemia on empty stomach of above 7.7 mmol/l one month after increasing the dosage of the traditional medicinal product. Or, there may be an undesirable event or abnormal laboratory result (or level 3 or 4 toxicity rate).

23. HYPERTENSION

The general objective is to evaluate the safety and efficacy of African traditional medicine (ATM) used for the management of hypertension. Specific objectives are to conduct the safety assessment and efficacy assessment of ATMs used for the management of hypertension and to compare the clinical efficacy and safety of African Traditional Medicine to a first-line orthodox anti-hypertensive medicine in the management of hypertension (this is applicable only in a comparative controlled clinical trial since it may not be appropriate to use placebo in the control group).

Table 1: Classification of blood pressure for adults aged 15 years and above

Blood pressure classification	Systolic blood pressure (mmHg)	Diastolic blood pressure(mmHg)
Normal	<120	and <80
Pre-hypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	>160	or >100

BLOOD PRESSURE DETECTION AND CONFIRMATION

The Consultative Meeting on Hypertension Control in the African Region, held in Harare in November 1999, recommended that the mercury manometer should continue to be the gold standard instrument for use in the primary health care centres where most of the initial diagnosis of hypertension are made. However, the same meeting, for research purposes, recommended the oscillometric digital manometers. Thus, for this trial, the digital manometer is recommended. The unit of measurement should continue to be the mmHg while the reading rate should be at 2 mmHg per beat instead of 5 mmHg per beat. The updated list of validated devices can be found at the web site: http://www.dableducational.com. Due to the variability of measurements of casual blood pressure, it is recommended that the subject be seated for 10 minutes in a quiet environment before the measurement is taken and repeated at one-minute interval. If there is a difference of more than 5 mmHg, then the measurement should be repeated. Self-measurement of blood pressure (or in pharmacies and clinics)

can be useful in monitoring the blood pressure and consequently eliminating the "white coat effect". A definitive diagnosis is crucial since wrong diagnosis may lead to a subject unnecessarily taking medications for a long time with attendant side-effects and cost implications. Indeed, the diagnosis, management, treatment and research on hypertension is dependent on an accurate measurement of blood pressure.

BIOLOGICAL INVESTIGATIONS

Urinalysis should also be carried out at each visit of the subject. Furthermore, blood electrolytes, glucose, cholestrol, urea, creatinine and ECG should be investigated at baseline and during therapy.

Patient education on non-pharmacological management

A trained nurse usually carries out education on this aspect and it is aimed at promoting the subject's compliance, which may subsequently lead to a significant decrease in medication or no medication.

The main components of patient education include reduction of salt intake, body weight, alcohol intake and stress and a concomitant increase in physical activity and intake of vegetables and fruits. The non-pharmacological management needs discipline and determination of the subjects guided by trained health personnel and takes time to yield tangible results.

Pharmacological management

The Consultative Meeting on Hypertension Control in the African Region recommended diuretics and beta-blockers, respectively, as the first- and second-line medicines against hypertension. Since the use of placebo is not recommended for hypertension, the control group should be given appropriate first- or second-line treatment in accordance with the assessment of the clinician in charge of the study.

Clinical evaluation

Blood pressure should not be assessed in isolation, but be a part of a comprehensive assessment that includes other risk factors of cardiovascular disease. Age, sex, smoking and alcohol consumption, physical activity, weight-height (body mass index), personal and family history of premature cardiovascular disease and other risk factors including diabetes should be recorded. According to Lemogoum et al (2003), clinical and laboratory evaluation of hypertensive patients should be conducted with four aims:

(a) To confirm a persistent elevation of blood pressure and determine the level;

(b) To determine the presence of target organ damage and quantify its extent;

(c) To search for other cardiovascular risk factors and clinical conditions that may influence the prognosis and treatment;

(d) To identify or exclude secondary causes of hyperte nsion.

In addition to taking history and doing full physical examination, the following standard routine laboratory investigations should be conducted:

(a) Urinalysis for blood, protein and glucose. Repeat test and carry out further tests if the results are positive;
(b) Microscopic examination of urine;
(c) Blood chemistry for potassium, creatinine, fasting and/or random glucose;
(d) Fundoscopy and ECG.

Further investigations to exclude secondary hypertension and target organ damage should be guided by history, examination and routine investigations.

Assessment of efficacy

It is important to specify the efficacy parameters as well as the methods and timing for assessing, recording and analysing them.

Assessment of safety

The specification of safety parameters, methods and timing for assessing, recording and analysing safety parameters should be considered prior to the commencement of the trial. Furthermore, the procedures for recording and reporting the adverse effects and inter-current illnesses should be clearly established. In addition, this section should contain the type and duration of the follow up of subjects after adverse events.

Schedule of visits for clinical and biological evaluation

The volunteers are expected to visit the health facility for an initial baseline clinical assessment, then monthly till the end of the study. Samples will be collected from the study participants at the baseline and then every month for biological evaluation. Appropriate laboratory investigation forms should be designed which will indicate the tests to be carried out and when the tests are to be conducted. The schedule of visits for clinical and biological evaluation may deviate from what has been suggested, depending on the national regulations on such matters and the realities on the ground.

End-points of the trial

Primary end-points

(a) Development of or delay in the development or resolution of symptoms
(b) Degree of quality of life (see details in Karnofsky Performance Scale, Annex 3).

Secondary end-points

(a) Significant changes in biological markers of the disease (e.g. haematological or immunological parameters).
(b) Development of drug-related toxicities sufficiently severe to warrant dose modification, interruption or permanent discontinuation.

ANNEX 1

INFORMED CONSENT FORM TEMPLATE FOR CLINICAL STUDIES

(These could be either clinical trials or clinical research)

(Language used throughout form should be at the level of a local student of class 6 or 8)

[INSTITUTIONAL LETTER HEAD]

[Name of Principle Investigator]
[Name of Organization]
[Name of Sponsor]

Information Sheet for [group of individuals] *(e.g. men and women attending the kidney clinic)*
Participating in the Research ["*Name of proposal*"]
(Version ———)

[Describe yourself and what you do]
(e.g. I am X, working for the Y Research Institute. We are trying to study Z disease, which is very common in this country)

PURPOSE:

[Explain the problem in lay terms]
(Use local and simplified terms for a disease, e.g. local name of disease instead of malaria, mosquito instead of anopheles, "mosquitoes help in spreading the disease" rather than "mosquitoes are the vectors" etc.)

The reason for doing this research is to find out [explain the research question in lay terms]
(Avoid use of terms like pathogenesis, indicators, determinants, equitable etc.)

[If the protocol is for a clinical trial, give the phase of the trial and explain what that means as well as why the drugs being compared are being compared]

(Include the following section only if the protocol is for a clinical trial)
Some Information about the trial drug:

[In lay terminology, provide information about the drug such as its manufacturer or location of manufacture, the reason for its development, and the class of chemicals to which it belongs]

[Explain the known experience with this drug]

(e.g. it has been found to be very safe in healthy volunteers but has not as yet been tested in persons who have this disease)

[Explain comprehensively all the known side-effects/toxicity of this drug, as well as the toxicity of all the other medicines that are being used in the trial]

(This section for any clinical study)
Procedures:

To find answers to some of these questions, we invite you to take part in this research project.

[Include the following paragraph only if the protocol is for a clinical trial involving randomisation or placebo or blinding etc.]

In order to answer this question without bias, the scientific method used divides all participants into two [or three or four] groups in such a way that each person has an equal chance of being in any of the groups (as in drawing lots, for example). One half of the group will get the medicine that we are studying (the test medicine), and the second half will get the medicine whose effect is already known [or an inactive substance, which the scientists call placebo] (the control medicine). So you have a 50-50 chance of receiving the new drug.

To help us know the true effect of the medicine, neither the doctors and scientists working on this research project nor the nurses will know who is in which group until the end of the research. This does not mean that the persons in the clinic/hospital looking after the participants will not know the condition of the participants' disease during this period. Indeed, they will keep a very close watch on the participants. When necessitated by a participant's condition or response to the treatment being studied, we can break this code and find out which medicines the participant has been getting. [If necessary, enumerate the conditions under which the code will be broken].

(Alternate phrasing: Sometimes because we do not know if the new drug is better than the currently available drug/drugs for treating this disease, we need to make comparisons. People taking part in this research will be put into groups and then compared. The groups are selected by a computer which has no information about the individual - i.e. by chance. Participants in each group then have a different treatment and these are compared).

You should tell the subjects what chance they have of getting the study treatment e.g. a one in four chance.

(Include the following paragraph only if the protocol is for a clinical trial)
Why should we use an inactive medicine or a control medicine? An inactive medicine or a placebo is sometimes used in research of this type to remove any bias and to find out the true contribution of the test medicine towards the cure of the disease that we are studying. A placebo is a dummy treatment such as a pill which looks like the real thing but is not. It contains no active ingredient.

(This section for any clinical study)
If you choose to participate, you will be required to [describe or explain the exact procedures that will be followed, the tests that will be done, and the medicines that will be given. Describe very clearly which procedure is routine and which is experimental or research.]
(e.g. In the first visit, a small amount of blood, equal to about a teaspoonful will be taken from a vein in your hand. This will be tested for the presence of substances (instead of antibodies) that help your body to fight infections.

(In case of a clinical trial)*You will then be given the test medicine, though, as explained earlier, neither you nor we will know whether you have received the test or the control medicine etc.*
(**In case of a clinical research**) You will receive the treatment of your condition according to national guidelines, etc.

The expected duration of the study is [length of study] days, and you will be required to come to the clinic/hospital/health facility [number of visits the participant will have to make] days, for [length of each visit] hours each day.

The following procedure(s) will be done upon each visit:
[Explain exactly what will be required upon each visit]

[If blood samples will be taken, then explain how many times and how much in a language that the person understands]
(e.g. blood equal to about one teaspoonful, as opposed to 5 ml However, it may be inappropriate to tell a tribal villager that blood equal to a wine-glass full will be taken).

[If a biopsy will be taken, then explain whether it will be under local anesthesia, sedation or general anesthesia, and what sort of symptoms and side effects the participant should expect under each category]

[If any other procedure will be carried out, then explain what to expect]

(Include the following paragraph only if the protocol is for a clinical trial)
[If the protocol includes the use of a rescue medicine, then provide information about the rescue medicine or treatment such as what it is and the criterion for its use]

(e.g. If we find that the medicine that is being used does not have the desired effect, or not to the extent that we wish it to have, we will use what is called a "rescue medicine." For example, in pain trials, if the test drug does not control pain, then intravenous morphine may be used as a rescue medicine).

(This section for any clinical study)
[If the tissues/blood samples or any other human biological material will be stored for a duration longer than the research purpose, or is likely to be used for a purpose other than mentioned in the research proposal, then provide information about this and obtain consent specifically for such storage and use in addition to consent for participation in the study] - (see last section)

If not, then explicitly mention here that the biological samples obtained during this research procedure will be used only for this research, and will be destroyed after ——— years, when the research is completed.

(Include the following section only if relevant)
Side Effects:

As mentioned above, these medicines can have some side effects or some effects that we are not aware of. However, we will follow you closely and keep track of the side effects and the toxicity. We may use some other medicines to decrease the symptoms of your toxicity or stop the use of one or more drugs. We will discuss with you, if this is necessary, and you will always be consulted before we move to the next step. *(This text is just an example; the text used will depend upon the trial. The research participants need to know what will happen in the event of a side effect or an unexpected event)*

RISKS AND DISCOMFORTS:

By participating in this research you are likely to experience some discomfort. [Explain the type and source of discomfort]
(e.g. the discomfort of repeated blood pressure readings or venepuncture).

By participating in this research you are likely to be at greater risk than you would otherwise be for [Explain the type of anticipated risk]. We will try to decrease the chances of any of these from events occurring, but if an untoward event does occur, we will provide you with [explain the level of care that will be available, who will provide it, and who will pay for it].

BENEFITS:

(Benefits may be divided into benefits to the individual, benefits to the community in which the individual resides, and benefits to society as a whole)

If you participate in this research, you are likely to have the following benefits: any interim illnesses will be treated at no charge to you. If your child falls sick during this period he/she will be treated free of charge. *(mention only those activities that will be actual benefits and not those to which they are entitled regardless of participation).*

There may not be any benefit for you but your participation is likely to help us find the answer to the research question. [Mention the answer(s) you are seeking].
There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.

INCENTIVES:

You will not be provided any incentive to take part in this research. However, you will be reimbursed with [provide a figure, if money is involved] for your lost time and your travel expense.

(OR)

As a form of appreciation for your time and input into the research, you will receive [enumerate exactly what will be provided].

Confidentiality:
[Explain how the research team will maintain the confidentiality of data, especially with respect to the information about the participant, which would otherwise be known only to the physician but would now be available to the entire research team]. *(Because something out of the ordinary is being done through research, any individual taking part in the research is likely to be more easily identified by members of the community and is therefore more likely to be stigmatized).*

The information that we collect from this research project will be kept confidential. Information about you that will be collected from the study will be stored in a file that will not have your name on it, but a number assigned to it instead. The name associated with the number assigned to each file will be kept under lock and key and will not be divulged to anyone except [name who will have access to the information, such as research sponsors, DSMB board, your clinician, etc].

Right to Refuse or Withdraw:
You do not have to take part in this research if you do not wish to do so, and refusing to participate will not affect your treatment at this center in any way. You will still have all the benefits that you would otherwise have at this center.

You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this center will not be affected in any way.

(Include the following section if the study involves administration of investigational drugs or use of new therapeutic procedures)
Alternatives to participating:

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the centre/institute/hospital.
[Explain the **established** standard treatment]

Who to Contact:
If you have any questions you may ask them now or later. If you wish to ask questions later, you may contact any of the following: [name, address/telephone number/e-mail]
(The contact person should be a "local"' person who can actually be contacted)

This proposal has been reviewed and approved by [name of the IRB], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact [name, address, telephone number]

Certificate of Consent
(This is an integral part of the information sheet and not a stand-alone document)

[In first person point of view *(e.g. I have been invited to take part in the research on etc. I have been told the purpose of this research study is etc),* briefly summarize the main items from the above statement in separate paragraphs in the following order:

Purpose *of the research.*
Procedures that will be followed, including the total time involved for the subject.
Risks and discomforts, including psychological and social risks, if any.
Benefits of the research, separated into "benefits to you" (the subject) and "benefits to others".
Compensation, if any, provided to research subjects.
Confidentiality of subject-specific information and how it will or will not be maintained.
Alternatives to participation.
Contact information.]

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a subject in this study and understand that I have the right to withdraw from the study at any time without in any way affecting my medical care.

Print Name of Subject
_____

Date and Signature of Subject
_____ __/__/__ *(dd/mm/yy)*

If illiterate

Print Name of Independent Literate Witness
(if possible, this person should be selected by the participant and should have no connection to the research team)

Date and Signature of Witness

___/___/___ *(dd/mm/yy)*

Print Name of Researcher

_____

Date and Signature of Researcher

_____

___/___/___ *(dd/mm/yy)*

(Include the following section if the research protocol calls for storage and future use of specimens)

Consent for Storage and Future Use of Leftover Specimens

If any of the specimens I have provided for this research project are left over when the project is completed (Tick **one** choice from each of the following boxes)

- ◆ I wish this leftover material to be destroyed immediately
- ◆ I give permission for this leftover material to be stored and used in future research but only on the same subject as the current research project
- ◆ I give permission for this leftover material to be stored and used in future research of any type.

AND

- ◆ I want this leftover material to be destroyed after ____ years.
- ◆ I give permission for this leftover material to be stored indefinitely

AND

- ◆ I want my identity to be removed from the left over specimens.
- ◆ I want my identity to be kept with the left over specimens

Print Name of Subject

_____

Date and Signature of Subject

_____

___/___/___ *(dd/mm/yy)*

If illiterate:

Print Name of Independent Literate Witness (if possible, this person should be selected by the participant and should have no connection to the research team)

_____

Date and Signature of Witness

_____

___/___/___ (*dd/mm/yy*)

Print Name of Researcher

_____

Date and Signature of Researcher

_____

___/___/___ (*dd/mm/yy*)

ANNEX 2

MODEL LEGAL AGREEMENT BETWEEN A RESEARCH INSTITUTE AND A TRADITIONAL HEALTH PRACTITIONER:

SAMPLE MEMORANDUM OF UNDERSTANDING

Dated this ..... day of..... THIS AGREEMENT made this ..... day....., ... between THE INSTITUTE (specify the name) (hereinafter called "The INSTITUTE" which expression shall, where the context admits, include agents, successors in office and assigns) of the one part and .....(hereinafter called the TRADITIONAL HEALTH PRACTIONER or "THP" which expression shall, where the context admits, include his agents, personal legal representatives and assigns) of the other part.

WHEREAS:

1. "The INSTITUTE" is a scientific and technologically-oriented public institution established to undertake research and development work into (among other things) medicines and pharmaceutical raw materials from traditional medical knowledge based on indigenous biodiversity.

2. The "THP" has acquired useful information, facts and knowledge in respect of the use of herbal products for the management, treatment and/or cure of .....and other aliments and he is engaged in the practice of herbal medicine.

3. The "THP" is willing to make these information, facts and discoveries in respect of the herbal products available to "The INSTITUTE" for use in the management and/or cure of ..... and other ailments for the overall benefit of the public.

4. "The INSTITUTE" has requested, and the "THP" has agreed to provide, services and information set out herein on herbal products for development and use in the management of ... ...and other ailments.

5. The "THP" is willing and has agreed to supply "The INSTITUTE" with herbal materials (in their compounded forms) for the treatment of .....
.....and other ailments for scientific identification, evaluation, analysis, development and/or improvement.

6. The "THP" hereby gives consent to "The INSTITUTE" and the "The INSTITUTE" hereby accepts to conduct research into, develop and process the said herbal products into suitable medicines in dosage forms for commercial and industrial utilization towards the management or treatment of .....and other ailments.

NOW THIS AGREEMENT WITNESSETH:

In consideration of the mutual covenants and agreements herein contained, the parties hereto do agree as follows:

1. The "THP" hereby permits "The INSTITUTE" to conduct research into, develop and process the said herbal products into standard medicines in dosage forms and to ensure due scientific evaluation, purification, standardization and safety of the said products for use in the management of .....and other ailments aforesaid.

2. The "THP" shall disclose to "The INSTITUTE" his existing collections of the plant or herbal materials in their compounded form at the moment (and fully subsequently) in respect of .....and other ailments for scientific identification, evaluation and development and literature search on such compounded plants/materials and shall at all times endeavour during the continuance of this Agreement to make available to "The INSTITUTE" any collection at his disposal upon request.

3. In the event that any of the medicinal plants has already been documented for the same disease which the "THP" uses to treat, or where "The INSTITUTE" has already obtained information from other THP(s) on the same plant, then "The INSTITUTE" shall duly inform the "THP" as such, giving the relevant literature references within fourteen (14) days.

4. "The INSTITUTE" engages the "THP" to procure, provide and keep on supplying samples, information, facts/ideas relating to and in respect of herbal products that will facilitate research and development towards the management of..... and other ailments.

5. The "THP" shall, as and when requested by "The INSTITUTE" and within a reasonable time after receiving such request, supply compounded plant samples for the scientific evaluation as "The INSTITUTE" shall specify, and diligently proceed with the preparation of such samples and deliver the same as required by "The INSTITUTE".

6. "The INSTITUTE" shall subject the various extracts and fractions obtained from the medical plants used to prepare the herbal products to scientific evaluation for safety and efficacy provided that and it is hereby agreed that "The INSTITUTE" shall in all events furnish the "THP" in writing with the result of every scientific test or analysis carried out on any herbal product/ material received from him.

7. "The INSTITUTE" shall diligently proceed at (state town, e.g. Dar-es-Salaam or Abuja) or such other designated places within and outside (state country, e.g. Tanzania or Nigeria) as "The INSTITUTE may determine to conduct research and development work into the evaluation, preservation, purification, standardization, safety and rational utilization of the herbal products and formulate the same into dosage form for commercial and industrial use, and to apply and obtain the grant of patent in respect of the products at the cost, expense and techniques of "The INSTITUTE" and in a manner mentioned hereinbefore in the preceding clauses.

8. "The INSTITUTE" shall apply for and obtain, or cause to be granted and obtained, the letters of patent on the products in the name of "The INSTITUTE" after the same has been developed and processed provided that the "THP's" name be included in the patent, subject to the conditions hereinafter set forth.

9. Either party shall use every reasonable means to protect, preserve and secure the interest and person of the other, and the efficacy and safety of the products, and shall not subject each other to public ridicule, adverse publicity and derogatory treatment during the subsistence of this Agreement.

10. The "THP" shall be at liberty to continue to use, apply and utilize the herbal products which he has prepared and/or may continue to prepare in future by his own technique, notwithstanding the fact that the same or similar product referred to "The INSTITUTE" does not guarantee the safety, purity and quality control or standard of such products. Nothing in this Agreement shall be construed as implying that the "THP" is prohibited from citing his relationship with "The INSTITUTE" in any advertisement of his practice if the consent of "The INSTITUTE" is first sought and obtained in writing in this regard.

11. Any information acquired by the "THP" in the course of his services, transactions and operations under this Agreement regarding the sample preparation process, research and development work and details of the formulae of the products shall be treated by him as secret and confidential and shall not be disclosed by him to any other person from company/organization without the consent and authority in writing of "The INSTITUTE" provided, and it is hereby agreed, that "The INSTITUTE" shall not unreasonably withhold such consent.

12. The "THP" shall not, during the continuance of this Agreement, be engaged in a transaction similar with the one here in evidence with any other person, firm, company or organization

anywhere in (name of the country) in respect of products of any description or kind similar to, or competitive with, those of "The INSTITUTE" without the prior consent, in writing, of "The INSTITUTE".

13. The ownership of and rights to obtain trade name or trademark and/or registration of designs in any products supplied by the "THP" to "The INSTITUTE" under this Agreement shall be vested in "The INSTITUTE" from the date of delivery by the "THP" to "The INSTITUTE" of the herbal products, and "The INSTITUTE" shall thereupon be at liberty to effect and be responsible for the registration and other protection rights of such formulated dosage(s) as it thinks fit, provided always that the discovery of the herbal products by the "THP" shall be acknowledged as such in the correspondence and literature/publications on the products as much as practicable and provided that, and it is hereby agreed, that the "THP" gives no warranty for the efficacy and safety of such resultant end-product.

14. The "THP" hereby covenants to make available to "The INSTITUTE" upon its observance of the terms contained in this Agreement, information and assistance relating to and in furtherance of research and development of the herbal product.

15. "The INSTITUTE" shall endeavour in every reasonable and proper way and to the best of its ability to publicize the result of its research and development (R&D) of the herbal product and, for that purpose, advertise the same in magazines, journals, periodicals, weeklies, newspapers or on radio and television, in such manner as may be necessary.

16. IN CONSIDERATION of the foregoing provisions, "The INSTITUTE" shall, at the point of commercialization of the product derived from the "THP" input, negotiate on behalf of the "THP" for some royalty of at least 10% of the profit to accrue to the "THP".

17. IN FURTHER CONSIDERATION of the services rendered by the "THP", the following conditions shall apply regarding termination of this Agreement:
    (a) Without prejudice to any other remedies "The INSTITUTE" may have against the "THP", "The INSTITUTE" shall have the right, at any time by giving three months' notice in writing to the "THP", to terminate the Agreement in any of the following events:
        (i) If the "THP" commits a deliberate breach of any of the terms of this Agreement which he refuses to rectify even upon demand;
        (ii) If the "THP" dies, compounds with his creditors, or takes or suffers any similar action in consequence of debts;
        (iii) If from any cause the "THP", in the reasonable opinion of "The INSTITUTE", is prevented from performing his duties described hereunder for a continuous period of six (6) months or for a total of eight (8) months in any period of twelve (12) calendar months;

(iv) If the "THP" is guilty of any conduct which, in the reasonable opinion of "The INSTITUTE", is prejudicial to "The INSTITUTE's" interest;

(v) If the "THP" purports to assign the burden or benefits of this Agreement PROVIDED that the floating of a company by the "THP" to undertake the practice of herbal medicine or for his practice, shall not be taken as a breach hereof, provided that "The INSTITUTE" is duly notified and its consent obtained in writing.

(b) If "The INSTITUTE" ceases to carry out research and development to deal in such medicines as previously mentioned, this Agreement shall terminate forthwith, unless the business or any part of it (being a part concerned in the manufacture or sale of such medicines or any class of them) has been transferred to any other organization, and the rights and obligations of the company hereunder have been assigned to that other organization, after one month's notice of such assignment in writing has been given by "The INSTITUTE" to the "THP".

(c) It is hereby agreed that where pursuant to clause 17(a) it shall not be practicable to effect personal service of notice to terminate on the "THP", "The INSTITUTE" shall be excused from giving such notice as aforesaid.

18. If "The INSTITUTE" shall fail in any of its obligations to the "THP", and remains in breach for ninety (90) days, the "THP" for the management of (specify the disease) ..... and other ailments and there are no promises, terms or conditions, obligations, oral, written, express or implied, other than those contained herein.

19. Subject to clause 17 (c) above, all previous Agreements and arrangements, if any, relating to the foregoing between the parties hereto are hereby superseded.

20. If any dispute arises as to the construction of the provisions of this Agreement or the implementation of its terms, the parties shall appoint one independent arbitrator, or constitute a panel of three (3) arbitrators who, in addition to other remedies available to him, may on the 90th day of the breach terminate this Agreement forthwith.

21. The "THP" or his personal representative shall, upon the termination of this Agreement, immediately deliver up to "The INSTITUTE" all facilities and property belonging to "The INSTITUTE", which may be in his possession or under his control.

22. This Agreement shall have effect in substitution for all previous Agreements and arrangements, whether written or oral or implied by "The INSTITUTE" and the "THP".

23. This Agreement shall not in any way constitute or be presumed to constitute a partnership between the parties hereto, or make them in any way liable as partners of or as agents for one another. The "THP" shall relate with "The INSTITUTE" as an independent contractor/partner.

24. The waiver by either party of any breach of any terms of this Agreement shall not prevent the subsequent enforcement of that term, and shall not be deemed a waiver of any subsequent breach, PROVIDED that a breach, once rectified, shall not, for any purpose whatsoever, be taken into account.

25. The Agreement embodies the entire understanding of the parties in respect of research and development. And for the purpose of this clause, the provisions of the (name of relevant national legislation) ..... shall apply.

SIGNED, SEALED AND DELIVERED BY:.....
for and on behalf of "The INSTITUTE"
IN THE PRESENCE OF:
Name: .....
Address: .....

Occupation: .....

SIGNED, SEALED AND DELIVERED BY THE CONSULTANT THP"

(TRADITIONAL HEALTH PRACTITIONER)

IN THE PRESENCE OF:

Name: .....

Address: .....

.....

Occupation : .....

ANNEX 3

KARNOFSKY PERFORMANCE SCALE

The Karnofsky Performance Scale is an assessment tool is used to assist clinicians and caretakers to measure the patient's ability to carry out activities of daily living, and should be noted at each patient visit. A report of Karnofsky scores may be helpful if a patient applies for disability benefits.

DESCRIPTION	%
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs and symptoms of disease	90
Normal activity with effort; some signs and symptoms of disease	80
Cares for self; unable to carry on normal activity or do work	70
Requires occasional assistance, but is able to care for most personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalization necessary; requires active support treatment	20
Moribund; fatal processes progressing rapidly	10
Dead	0

ANNEX 4

DECLARATION OF HELSINKI*

Recommendations guiding physicians in biomedical research involving human subjects

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission. The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient". The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared recommendations [indicated below] as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

*Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989.

I. Basic principles of biomedical research involving human subjects

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by a careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from

participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with clinical care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being,it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients—for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

IV. Model list of items to be contained in a clinical trial protocol

The trial protocol should, where relevant, be required to cover the following points:

1. Title and justification for the trial.

2. Statement of rationale, objectives and purpose of trial.

3. Brief description of the site(s) where the trial is to be conducted

4. Name and address of the sponsor.

5. Name, address and qualifications of each investigator.

6. Description of the type of trial (randomized, blinded, open), trial design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), and method of and procedure(s) for randomization.

7. Description of trial subjects (criteria for inclusion and exclusion of potential subjects), process of recruitment, types, method(s) and timing of allocation of subjects into investigational groups.

8. Number of trial subjects needed to achieve the trial objective, based on statistical considerations.

9. Description of and justification for the route of administration, dosage, dosage interval and treatment period for the investigational and comparator products, if used. Dose-response relationships should be considered.

10. Any other treatment that may be given or permitted concomitantly.

11. Clinical and laboratory tests, pharmacokinetic analysis, etc., that are to be carried out.

12. Description of how responses are recorded (description and evaluation of methods and frequency of measurement), follow-up procedures and measures to determine the extent of compliance with the treatment among trial subjects.

13. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.

14. Methods for recording and reporting adverse events or reactions, and provisions for dealing with complications.

15. Procedures for the maintenance of subject identification code lists, treatment records, lists for the randomization of subjects and/or case-report forms (CRFs). Records should permit identification of individual patients or participants as well as auditing and reconstruction of data.

16. Information about how the trial code is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency.

17. Measures to be implemented to ensure the safe handling and storage of investigational and comparator products, if used, and to promote and determine the extent of compliance with the prescribed treatment and other instructions.

18. Description of methodology to be used to evaluate the results, (including statistical methods) and to report on patients or participants withdrawn from the trial.

19. Time schedule for completion of the trial.

20. Information to be presented to the trial subjects, including how they will be informed about the trial, and how and when their consent will be obtained.

21. Instructions for staff involved in the trial, including how they are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.

22. Ethical considerations and measures relating to the trial.

23. Medical care to be provided after the trial, modalities of post-trial treatment.

24. When the protocol serves as a contract, statements regarding financing, insurance, liability, delegation or distribution of responsibilities, and publication policy.

25. List of literature referred to in the protocol.

ANNEX 5

CLINICAL RESEARCH

GENERAL CONSIDERATION

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 4). 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 given here provides further details on the relevant sections dealing with clinical trials in the assessment of herbal medicines and traditional procedure-based therapies.

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, such 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:

(a) Evaluate traditional medicine in its own theoretical framework (e.g. mechanistic studies);

(b) Evaluate traditional medicine in the theoretical framework of conventional medicine (e.g. mechanistic studies);

(c) Compare the efficacy of different systems of traditional medicine and/or conventional medicine;

(d) Compare the efficacy of different traditional practices within a system of traditional medicine.

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. When 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. However, review of literature pertaining to traditional medicine may be difficult, due mainly to the lack of large clinical trials of good quality. In addition, the efficacy of particular treatment may also vary according to the skill and experience of the practitioner. These issues must be considered and kept in mind.

Selection of study design

Clinical research aimed at evaluating 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 4). The conventional concepts of clinical research design may be difficult to apply when using clinical research to evaluate various systems and practices of traditional medicine, depending on the goal of the assessment. In such circumstances, the choice of the 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, including the following:

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 design 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 in his or her own control. The 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 the "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 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 and 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 the efficacy of traditional medicine can be significantly increased by well-designed observational studies.

STUDY OUTCOME MEASURE

It is essential that the outcome measures chosen be appropriate to the research question. Appropriate outcomes may include both 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 large 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 or 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 reliability 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 a use of a herbal medicine or traditional procedure-based therapy and the prevention, diagnosis, improvement or treatment of an illness, provided that 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 the following (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 the treatment is valuable over and above what might be achieved by a control treatment and not whether the treatment is valuable at all. Thus, it allows researchers to distinguish the specific from the non-specific effects of the 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 the traditional ones. However, in some cases, placebo-controlled trials may not be possible.

It is preferable to use 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 black-box design, above).

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 the 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 it may help improve their quality of life. The *WHO Quality of Life 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.

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's approval, the following information regarding study outcomes should be clearly provided:

(a) Description of the therapeutic intervention;
(b) Description of the reasons for the selection of the therapeutic intervention;
(c) Description of the rationale for the choice of the study outcomes;

(d) Description of the outcome measurements, including a review of the validity and reliability of the measurements;

(e) A comprehensive protocol for taking the measurements (including how and when the measurements were taken);

(f) A clear statement of which expected outcomes the statistical method was based on.

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

ANNEX 6

SAMPLE OF A SUMMARY CASE-REPORT FORM

Subject report number: ..... Full name: .....

Physical address: .....

Sex: M / F Age:.....(years / months) Weight: .....kg

Previous antimalarials: Y / N / Unknown Drug:.....Dosage: .....

Day:	0	1	2	3	4	5	6	7	14	21	28
Date											
Danger signs											
Not able to drink											
Vomiting everything											
Convulsions											
Lethargic / unconscious											
Unable to sit / stand											
Symptoms											
History of fever (last 24 hrs)											
Rigors											
Headache											
Joint pains											
Weakness											
Tiredness											
Dizziness											
Appetite (↓, N, ↑)											

Nausea											
Vomiting											
Other (specify)											
Side-effects:											
Examination											
Axillary temperature											
Treatment given **Reasons for exclusion or loss to follow-up**											

OVERALL ASSESSMENT:

ETF / LTF / ACR / Exclude / Loss to follow-up

ANNEX 7

CHECKLIST OF POSSIBLE SIDE-EFFECTS

Day:	0	1	2	3	4	5	6	7	14	21	28
Nervous system:											
Drowsiness											
Nervousness											
Insomnia											
Nightmares											
Shakiness											
Numbness											
Tinnitus											
Blurred vision											
Unpleasant taste											
Thirst											
Cardiovascular:											
Fast heartbeat											
Irregular heartbeat											
Respiratory:											
Cough											
Chest pain											
Stuffy nose											
Gastrointestinal:											
Heartburn											
Abdominal pain											
Diarrhoea											
Constipation											

Intestinal wind											
Black stools											
Genito-urinary:											
Dysuria											
Nocturia											
Dark urine											
Change in sexual ability / desire											
Muco-cutaneous:											
Skin rash											
Pruritus											
Easy bruising											
Dry mouth											
Others (specify):											
Jaundice											

ANNEX 8

SAMPLE ADVERSE EVENTS RECORD

Subject record number: .....

Date that event started:.....**Date that event stopped:** .....

Severity of adverse event:

- Mild, tolerable, patient up and about
- Moderate, causes discomfort, but patient is up and about
- Severe, interferes with the patient's activities
- Fatal

Nature of adverse event: *Describe symptoms, system by system, using previous checklist as a guide*

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CAUSALITY:

- Definitely NOT caused by the herbal preparation
- Possibly caused by the herbal preparation
- Probably caused by the herbal preparation
- Definitely caused by the herbal preparation

Did this adverse event cause withdrawal from the study? Y / N

ANNEX 9

TOXICITY GRADING SCALE

ALLERGY	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SYMPTOMS	Asymptomatic, easily tolerated, transient	Mild tolerable symptoms, short duration, normal activity	Moderate symptoms, poorly tolerated, sustained, interferes with normal activity	Severe symptoms, intolerable, sustained, incapacitating, life threatening, fatal, permanently, results in congenital abnormalities, cancer, overdose
TRAITEMENT	Not required	Not required except when noted	Required, responds to Rx	No response to Rx, hospitalisation required
ALLERGY	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
ALLERGIC REACTION	Transient	URTICARIA, DRUG FEVER >38° C, 100.4°F. Mild bronchospasm	Serum sickness, bronchospasm requiring parental Rx	Anaphylaxis with hypotension
FEVER WITH DRUG (Absence of infection)	37.1-38°C, 98.7-100°F	38.1-40°C, 100.5-104°F	>40°c, >104°F FOR>24 hours despite antipyretic Rx	>40.°C, >104°F despite Rx for >24 hours, or any fever associated with hypotension
CARDIOVASCULAR	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
CARDIAC SYMPTOMS	Mild or transient	Symptoms on exertion, recurrent or persistent, no Rx required	Symptoms at rest, requires Rx	Severe symptoms, unresponsive to Rx
ARRHYTHMIA	Asymptomatic, transient, no Rx required	Recurrent or persistent, no Rx required	Requires Rx	Requires monitoring; or hypertension, or ventricular tachycard or fibrillation
CARDIAC BIOPSY (Index)	0.5	1.0	1.5	>1.5
CARDIAC FUNCTION	Asymptomatic, decreased ejection fraction by 20% of baseline	Asymptomatic decreased ejection fraction by >20% of baseline	Mild CHF, responsive to Rx	Severe refractory CHF

CARDIOVACULAIRE cont.	GRADE 1	GRADE 2	GRADE 3	GRADE4
OEDEMA (e.g.Peripheral capillary leak syndrome) also see Pulmonary	Minimal ankle pitting oedema	Ankle pitting oedema and weight gain 5kg	Peripheral oedema, weight gain 5-10kg, pleural effusion with no pulmonary function deficit	Anascara, severe pleural effusion with pulmonary function deficit, ascities, pulmonary oedema, weight gain>8kg.
HYPERTENSION	Asymptomatic, transient increases 20mm Hg or 150/100 if previously WNL. No Rx required	Recurrent or persistent (>1 hr) 20mm Hg or 150/100 if previously WNL. No Rx required	Persistent increase >20mm Hg or >150/100 if previously WNL. Rx required	Hypertension crisis
HYPERTENSION	10-20% decrease, systolic, no Rx required (includes transient orthostactic	21-50% decrease systolic, requiring fluids or other Rx but no hospitalisation	21-50% decrease systolic, requires pressors and hospitalisation, resolves within 48 hours	>50% decrease systolic, requiring hospitalisation, unresponsive to pressors, requires >48 hours to resolve after stopping agent
ISCHAEMIA	Non-specific T-wave flattening; stable EKG	Asymptomatic, EKG change; ST and T-wave change suggests ischaemia	New onset angina without evidence of infraction; clinical signification EKG	Acute EKG change diagnostic for myocardial infraction
PERICARDIAL EFFUSION	Asymptomatic, No Rx required	Pericarditis (rub, chest pain, EKG changes)	Symptomatic; large effusion, drainage required, no tamponade, responsive to drainage	Large effusion, temponade, drainage urgently required
CNS	**GRADE 1**	**GRAGE 2**	**GRADE 3**	**GRADE 4**
AFFECT ABNORMALITY	Transient panic/apathy; Mild anxiety/depression	Sustained panic/apathy; Moderate anxiety/ depression	Sustained panic/apathy; severe anxiety/depression; Requiring Rx	Sustained panic/apathy; Unreason to Rx; Suicidal ideation
ATAXIA 9Cerebellar)	Mild/transient gait or limb ataxia; slight incoordination, dysdiachokinesia	Intention tremor, nystagmus, dysmetria	Moderate gait or limb ataxia	Disabling ataxia, cerebella necrosis
AUTOMATIC DYSFUNCTION	Abnormal sweating	Impotence	Asymptomatic arrhythmia, orthostatic hypertension	Symptomatic arrhythmia, orthostatic hypertension

BLADER DYSFUNCTION		Dysfunction not requiring catheter	Dysfunction requiring catheter	Dysfunction requiring permanent catheter
COGNITIVE DEFFECT	Slow, accurate	Impaired memory or new learning	Global deficiency	Unresponsive
CONSTIPATION AUTOMATIC	Mild, no Rx required	Occasionally requiring cathartics	Daily cathartics/enema required	Abdominal distension, vomiting; Ileum>96 hours
CNS cont.	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
CORTICAL	Mild somnolence or agitation, easily arousable	Moderate somnolence or agitation ; responds to loud verbal or tactile stimuli	Severe somnolence, agitation, confusion, disorientation, or hallucinations ; responds to pain only	Coma, grand male seizures (current), toxic psychosis
FOCAL SEIZURES	Isolated	<2 per day	>3 per day	Status epileptics
GENERALISED SEIZURES	Isolated	<2 per day	>3 per day	Epilepsy partials continus
HEADACHE	Mild	Moderate or severe but transient	Unrelenting and severe	
HEARING LOSS	Transient decrease, loss by audiometer only	Tinnitus, moderate loss	Interferes with functions, correctable	Deaf, despite hearing aid
LANGUAGE ABNORMALITY	Inattentivness, slurring	Motor or communicative aphasia <2 hours	Motor or communicative aphasia >hours	Global aphasia
MOTOR DEFICIT	Mild/transient subjective weakness	Moderate objective weakness, ambulatory	Non-ambulatory; objective weakness	Complete paralysis
MOVEMENT DISORDERS	Transient abnormal limb movement	Moderate limb/gait disorder	Severe and reversible parkinsonism, dystonia or tremor	Permanent parkinsonism dystonia or tremor
SENSORY DEFICIT	Mild parenthesis, decreased DTR's	Mild to moderate objective sensory loss; absent DTR's moderate	Severe paresthesia, severe objective sensory loss; interferes with function	Complete loss of sensation

SPEECH ABNORMALITY	Mild slurring	Moderate slurring	Unintelligible	Mute
VERTIGO	Mild, transient	Moderate, nausea	Associates with nausea and vomiting	Disabling intractable
VISION ABNORMALITY	Slightly reduces acuity	Symptomatic, correctable	Symptomatic, unable to correct	Blind
DERMATOLOGIC	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
ALOPECIA	Partial loss	Complete loss	Non-reversible	
CHEILITIS	Chapping	Fissures	Bleeding	Necrosis
SKIN REACTION	Dry skin, mild or transient rash, scattered asymptomatic macular or papular eruption or erythema	Dry desquamation, scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Moist desquamation, bullous disease, generalised symptomatic macular, papular or vesicular eruption	Exfoliate dermatitis; requires surgical Rx
GASTROINTESTINAL	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
DIARRHOEA	Transient, >2-3 stools per day over baseline	Tolerable, >4-6 stools per day over baseline, or nocturnal stools, moderate cramping	Intolerable, >7-9 stools per day over baseline, or incontinence, severe cramping	Haemorrhagic, >10 stools per day over baseline, dehydration, requires parenteral Rx.
NAUSEA	Able to eat, reasonable intake	Able to eat, decreased intake	No significant intake	
VOMITING	1 x in 24 hours	2-5 x in 24 hours	6-10 x in 24 hours	>10 x in 24 hours, or requires parenteral support
STOMATITIS	Milk soreness, erythema, painless ulcers	Painful erythema, patchy oedema or ulcers, but can eat	Confluent ulcers, painful erythema, necrosis, requires parenteral or entereal support	Haemorrhagic ulceration, necrosis, requires parenteral or entereal support

GENERAL	GRADE 1	GRADE 2	GRADE 3	GRADE 4
MYALGIA CHILLS	Myalgia Mild	Myalgia requiring treatment Moderate	Severe, CK 2.0-5.0 X ULN	Intractable, CK >5 x ULN
LOCAL	Pain	Pain and swelling, inflammation or phlebitis	Ulceration	Plastic surgery indicated
HAEMATOLOGICAL	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Anaemia (Hg/g)	10 - normal	8.0 - 10	6,5 – 7,9	<6.5
GRANULOCYTOPENIA (X 10 mL)	1-5.9 and >20% decrease from baseline	1.0- 1.4and >35% decrease from baseline	0.5 – 0.9 and >50% decrease from baseline	<0.5 and >75% decrease from baseline
LEUKOPOENIA (X10 ml)	3.0 – 3.9 and >20% decrease from baseline	2.0 – 2.9 and >35% decrease from baseline	1.0 – 1.9 and >50% decrease form baseline	<1.0 and > 75% decrease from baseline
THROMBOCYTOPOENIA (X10 mL)	75-99 and >20% decrease from baseline	50-74 and >35% decrease from baseline	25-49 and >50% decrease from baseline	<25 and >75% decrease from baseline
HAEMORRHAGE	Petechiae, minimal blood loss, no transfusion required, mild	Gross, transfusion required, 1-2 U	Gross, transfusion required 3-4 U	Massive transfusion required, e"4 U
HAEPATIC	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
ALKALINE PHOSPHATASE INCREASE	1.5 –2.5 X ULN1	>1.5 – 2.5 X ULN1	>5.0 – 10.0 X ULN1	>10.0 X ULN1
BILIRUBIN INCREASE		1.3 – 1.5 X ULN1	>1.5 – 3.0 X ULN1	>3.0 X ULN1
HEPATIC SYMPTOMS			Pre-coma	Hepatic Coma
TRANSMINASE INCREASE	1.5 – 2.5 X ULN1	>2.5 – 5.0 X ULN1	>5.0 – 20 X ULN1	>20 X ULN1

INFECTION	GRADE 1	GRADE 2	GRADE 3	GRADE 4
INFECTION	Mild Infection, Unknown origin	Moderate infection	Major organ infection	Disseminated infection, multi-lobar pneumonia, life-threatening sepsis
FEVER	37.1-38°C	38.1-40°C	>40°C, >104°F for 24 hours despite antipyretic Rx	>40°C, >104°F for >24hours or a fever associated with hypotension
PULMONARY	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
PULMONARY FUNCTION ABNORMALITY	FVC 70-80% of predicted FEV, or DLCO 60-80% of predicted; 15-25% decrease from abnormal baseline	FVC 50-69% of predicted FEV, or DLCO 40-59% or predicted; 50% decrease from abnormal baseline	FVC <50% of predicted FEV, or DLCO <40% of predicted; 50% decrease from abnormal baseline	Unable to perform test due to respiratory distress
RESPIRATORY SYMPTOMS	Mild or transient, asymptomatic with PFT (Pulmonary Function Tests) abnormal	Dyspnoea on significant exertion	Symptoms during normal activity; persistent Dyspnoea	Severe symptoms at rest, non-responsive to Rx
CHEST X-RAY	<10% lung fields show infiltrate or effusion	10-20% lung fields show infiltrate or effusion	21-50% lung fields show infiltrate or effusion	>50% lung fields show infilterate or effusion
ABG	PAO2 <95 on room air	PAO2 <80 on room air	PAO2 <60 on room air	PAO2 <60 on supplemental oxygen
RENAL	**GRADE 1**	**GRADE2**	**GRADE 3**	**GRADE 4**
CREATININE INCREASE (mg/dL)	1.25-2.5 X ULN1	>2.5-5.0 X ULN1	>5.0-10.0 X ULN1	>10 X ULN1; requiring dialysis P8.0), irreversible loss of >20%
CLACULATED CREATININE CLEARANCE	70-80% of baseline	50-69% of baseline	30-49% of baseline	<30% of baseline
DYSURIA	Mild	Moderate	Severe	
HAEMATURIA	6-10 RBC/HPF2	11-50 RBC/HPF2	>50 RBC/HPF2	Requires transfusion

PROTEINURIA	1; <3.0g%, <3g/l	2-3; >0.3-1. 0g%, 3-10gl	4; >1.0G%, >10g/l	Nephritic syndrome
METABOLIC	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
HYPERGLYCAEMIA	140-160MG/dL	161-250MG/dL	251-500mg/dL	500MG/dL; ketoacidosis
HYPOGLYCAEMIA (Random)	55-64ML/dL	40-54mg-dL	30-39MG/dL	>30MG/dL
MYLASE	>1.5 XUNL1	1.5-2.0 XUNL1	2.1 –5.0 XULN1	>5.0 XULN1
HUPERCALCAEMIA HYPOCLACAEMIA HYPOMAGNESEMIA	10.6-11.5MG/dL 8.4-7.8mg/dL 1.4-1.2mg/dL	11.6-125MG/dL 7.7-7.0MG/dL 1.1-0.9mg/dL	12.6-13.5MG/dL 6.9-6.81MG/dL 08-06mg/dL	>13.5MG/dL >6.1MG/dL £0.5mg/dL
HYPOALBUMINEMIA	2.8mg/dL	2.4-2.7mg/dL	2.0-2.3mg/dL	£2.0mg/dL
COAGULATION	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
FIBRINOGEN	0.99-0.75 XUNL1	0.74-0.5 XUNL1	049-0.25 XUNL1	£0.24 XUNL1
PROTHROMBIN TIME	1.1-25 XULN1	1.26 XULN1	1.51 –2.0 XULN1	>2.0 XULN1
PARTIAL THROMBOPLASTIN TIME	1.1 – 1.66 X UNL1	1.67-2.33 XULN1	2.34.3.0 XULN1	>3.0 X ULN1

Key

1. ULN – Upper Limit of Normal
   RBC/HPF – Red Blood Cells/High Power Field

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