Operational guidance: Information needed to support clinical trials of herbal products

UNICEF/UNDP/World Bank/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)

TDR/GEN/Guidance/05.1

Design and layout: Lisa Schwarb

Operational guidance: Information needed to support clinical trials of herbal products

UNICEF/UNDP/World Bank/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)

CONTENTS

1. | INTRODUCTION

Herbal and other traditional pharmacologic therapies are in widespread use throughout the world. Such widespread use suggests, but does not assure, that traditional medicines have a favourable risk-benefit ratio. Rather, traditional medicines may be regarded as a rich source of potentially attractive therapies. The actual benefits and risks remain to be evaluated by clinical trials supported and conducted according to the principles of modern clinical science.

Justification for a clinical trial of a conventional drug involves four sets of issues: chemical-manufacturing-control (CMC) issues, non-clinical issues, clinical issues, and ethical issues. Two unique characteristics of herbal products are that they are multi-component mixtures, and that substantial prior human use precedes their formal investigation. These features have important ramifications for CMC, non-clinical, clinical, and ethical issues.

International organizations and national authorities have published statements for supporting clinical trials of herbal products, in which the justification required for conventional drugs has been adapted to the particular case of traditional medicines.

These statements tend to be broad in their coverage, very detailed, and often out of date. In addition, national statements focus on the regulatory requirements and languages of individual countries. There is a need for an international organization such as WHO-TDR to issue clear and concise recommendations for the data needed to support clinical trials in which herbal products are evaluated for diagnosis or treatment of diseases.

The target audience for these recommendations is primarily the community of clinical investigators wishing to evaluate the benefits and risks of herbal products. The secondary audience is national regulatory authorities. The following recommendations are written in broad terms so as to be useful for clinical investigators as well as to be compatible with the global regulatory climate. It is hoped that these recommendations will lead to well supported clinical trials of traditional herbal products, approvable by national regulatory authorities, and thus lead to improved chances of determining which herbal products are effective and safe for clinical diseases.

2. | CHEMISTRY-MANUFACTURING-CONTROL (CMC) CONSIDERATIONS FOR HERBAL PRODUCTS

For conventional, chemically-defined drug products, general considerations are synthesis and/or purification of the active pharmaceutical ingredient (API), manufacturing of the product that is administered to the patient, and control of these processes so that the API and product are made reproducibly. Since herbal products are manufactured from plant material, these considerations have to be translated into terms appropriate to this plant source.

2.1. | Overview of CMC evidence needed to support clinical trials for herbal products

2.1.1. Unlike standard chemically-defined drugs, herbal products have often had substantial human use prior to clinical trial evaluation. To capitalize on the use of this information in protocols to evaluate these products, it is important that the chemistry, manufacturing, and control of the product to be used mimics that for the traditionally-used formulation.

2.1.2. Also unlike conventional drugs, herbal products are mixtures of at least partially uncharacterized constituents. It is postulated that being a mixture provides a therapeutic advantage, in that unknown constituents may combine in an additive or synergistic fashion with known constituents to provide more efficacy than would be provided by the known constituent alone. Thus, evaluation of herbal products does not require attempts to purify the medicines down to known or otherwise single chemical constituents.

2.1.3. For herbal products, "analysis of the active pharmaceutical ingredient(s)" may be best approached by analysis of one or more hypothesized active ingredient(s), analysis of a chemical constituent that constitutes a sizable percentage of the total ingredients, and a chemical fingerprint of the total ingredients. The latter two analyses are surrogates for analysis of the unknown constituents that contribute to efficacy.

2.1.4. Specifications for acceptable values of analytic data should reflect the best available standards. For herbal products, variation of content from batch to batch may be an issue, and several analytical procedures may be needed to adequately quantify their constituents.

2.1.5. Because herbal products are sourced from plants, levels of contaminating herbicides and pesticides as well as toxic contaminations must particularly be addressed. The presence of adulterants should also be considered.

2.1.6. Many herbal medicines are in fact polyherbal. Plants may either be mixed before extraction or the extracts may be combined. In either case, information on each individual plant species used must be collected.

2.1.7. Herbal products intended for administration to humans are clinical trial materials, and they should therefore be made following the principles of GMP. Indeed, in many countries, the facilities have to have a current certificate of GMP.

2.2. | Information needed to support a clinical trial for a herbal product

2.2.1. Information on the herbal product proposed for phase 1/2 studies

Phase 1/2 trials are performed on few subjects under tight medical supervision. While details on specification and quality control of the product used for the trial are required, GMP standards for CMC processes may, in general, not be required at this stage.

HERBAL SUBSTANCE:

- description of the plant: genus, species (cultivar where appropriate); region(s) and country(ies) of origin; time of harvest; parts to be harvested
- plant processing: drying, mechanical disruption, solvent extraction (aqueous or organic solvents, others)
- analytical procedures
- specification
- storage conditions/shelf life.

HERBAL PRODUCT:

- amount of active ingredient
- list of excipients
- type of product (tablet, capsule, etc.) and its method of manufacture
- analysis of putative active ingredient(s) via chemical or biological parameters
- analysis of a sizeable chemical constituent (analytical marker compound)
- analysis via chemical fingerprint (analytical markers)
- analysis for lack of contamination by pesticides, herbicides, heavy metals, synthetic drug adulterants, microbials, toxins, etc.

- dissolution studies
- storage conditions and stability over the length of the trial
- specification against which a certificate of analysis can be assessed before the clinical trial material is released.

2.3. | Information on the herbal product proposed for phase 3 studies

Phase 3 trials are performed on large number of patients and are often carried out prior to registration and general use. Therefore, GMP standards are needed prior to phase 3 trials. In practice, this means performing generally the same procedures as for phase 1/2 trials, but more extensively and with more stringent oversight.

HERBAL SUBSTANCE:

- as above for phase 1/2 trials.

In addition:

- statement that the plant is cultivated according to Good Agricultural Practices or harvested according to Good Wildcrafting Practices
- reference batch.

HERBAL PRODUCT:

- as above for phase 1/2 trials.

In addition:

- environmental impact statement.

3. | NON-CLINICAL CONSIDERATIONS FOR HERBAL PRODUCTS

3.1. | Introduction: Information needed for a conventional drug

Non-clinical information generally needed to support a clinical investigation of a conventional drug consists of data on efficacy, toxicity, and pharmacokinetics.

Efficacy is demonstrated in enzyme/receptor assays, in vitro, and in animal models.

Toxicity is investigated:

- *in vitro* and in mice to assess genotoxicity
- *in vitro* to assess cytotoxicity
- in rodents to assess single-dose acute toxicity and maximum tolerated dose
- in one rodent model and one non-rodent model to investigate repeat dose (1, 3, 6, 9 months) toxicological effects
- in a rodent model and in the rabbit to assess reproductive toxicity
- in the rat to assess carcinogenicity.

Pharmacokinetic analyses relate to:

- absorption of the drug from the gut after e.g. oral dosing, or mobilization from the injection site after injection
- distribution of the API around the body
- rate of drug metabolism, the metabolic enzyme involved, and the nature of the metabolites produced.

3.2. | Information needed to support a clinical trial for a herbal product

3.2.1. Efficacy

It is recommended that the appropriate literature sources be searched for all available evidence on efficacy. Examples of such sources are medical and scientific journals, pharmacopeia, and articles on traditional medicines. Only if there are obvious gaps in the information or the total amount of data is insubstantial should it be necessary to perform new efficacy experiments.

3.2.2. Toxicology

It is imperative that the appropriate literature sources (as above) be reviewed for the toxicities of the herbal products in prior human experiences or existing animal data. The need for additional non-clinical studies prior to clinical trials depends on the following considerations:

- similarities between the new and old preparations, in terms of product characteristics, and usages in clinical settings.
- scale and exposure (dosage/duration) of the proposed new clinical studies.
- frequency and severity of any known toxicity.

Thus, in general, requirements for non-clinical studies may range from none for early phase, small, studies using the same preparations that have been used extensively and without known safety problems, to a complete set of conventional toxicology studies for relatively new products in large phase 3 trials. For many herbal products, certain non-clinical studies may be necessary but can be conducted concurrently with the proposed clinical trials.

3.2.3. Pharmacokinetics

It is technically difficult to work in this area as often the APIs are unknown and there are likely to be a large number present. Also, the dosing regimen needed for the clinical studies can be deduced from traditional methodology, rather than deduced from animal pharmacokinetics. Therefore non-clinical pharmacokinetics is not absolutely required.

4. | CLINICAL CONSIDERATIONS FOR HERBAL PRODUCTS

Good Clinical Practice should be applied in all stages of clinical trials to ensure that quality and ethical requirements for clinical studies are met. It is expected that a traditional practitioner familiar with the product proposed for investigation be an integral member of the protocol development team, where those traditional practitioners exist. For all clinical trials, biostatisticians should be consulted to ensure that the sample size is sufficient to satisfy the primary endpoint/objective.

4.1. | Introduction: Information needed for a standard intervention

Phase 1 studies are designed to determine safety associated with increasing doses in normal volunteers, as a precursor to phase 2 and phase 3 trials. In addition, phase 1 studies investigate toxicity and drug levels in states in which drug levels might be altered: the fed vs. the fasted state, in renal or hepatic impairment. Mechanisms of action are also investigated in phase 1.

Phase 2 studies evaluate the efficacy of a range of dosages in individuals with disease. Phase 2 studies typically start by evaluating the maximum tolerated dose determined in the prior phase 1 normal-volunteer studies. If this dose is effective, dose-ranging downwards would be investigated. If the phase 1 dose is ineffective, it is possible that higher doses will demonstrate efficacy and only mild intolerance, so dose-ranging upwards may be performed. Phase 2 dose-ranging studies utilize a relatively small number of patients per dosage group. Placebo and standard intervention groups may be included. If surrogate markers rather than disease endpoints are used in the phase 2 studies, it may be necessary to repeat dose-ranging in phase 3 trials with more valid disease endpoints.

Phase 3 studies are expanded trials of safety and efficacy. They are performed after preliminary evidence suggesting efficacy for the intervention has been obtained, and are intended to gather the additional information about efficacy and safety that is needed to evaluate the overall benefit-risk ratio of the intervention and to provide an adequate basis for general clinical use. Phase 3 studies usually include large numbers (several hundred to several thousand) of subjects, may involve human populations with broader entrance characteristics than were used in the phase 2 trials, and involve statistical comparison of the intervention to standard and/or placebo interventions.

4.1.1. Important note on phase 1, phase 2, and phase 3 trials

Phase 1 studies in normal volunteers are generally unnecessary for herbal traditional medicines. The substantial prior human use of traditional dose regimens of herbal medicines generally conveys reasonable confidence that these regimens can safely be administered to small numbers of carefully monitored clinical subjects in phase 2 trials.

Care should be taken that phase 3 trials are not undertaken prematurely, but are instituted only after dose-ranging phase 2 data are available. The purpose of a clinical trial is to evaluate an intervention for a clinical condition. Positive (or negative) data can lead to a recommendation to use (or not to use) the treatment. Use of a suboptimal dose that is safe but ineffective does not serve the needs of the community. Although the trial indicates only if the particular tested dose of the intervention was ineffective, the community may conclude that all doses of the intervention are ineffective, and patients will be denied possible benefits from the intervention. The inappropriate rejection of an intervention, "because phase 2 studies did not preceed a phase 3 trial, and a suboptimal dose was used in the phase 3 trial", is common for herbal medicines.

For some herbal products, there may exist previous research that has determined the optimum dose for a treatment. For others, dose-ranging phase 2 studies will need to be performed prior to beginning more extensive phase 3 studies. Therefore, if the scientific literature does not contain scientifically valid dose-ranging data, the investigator should first perform phase 2 trials to generate these data.

For dose-ranging studies, clinical investigators should consult biostatisticians for examples of dose-ranging schemes, and decide which scheme best fits the needs of the particular clinical problem.

4.2. | Information needed to support phase 2 trials

Although data from prior human experience may suggest confidence in the clinical safety of the product, it is important to verify tolerance in phase 2 trial patients. Both the literature review and the provisions in the protocol to be performed should focus on complete review of the clinical safety parameters. Examples of safety parameters are:

Organ system	Safety parameter
Neurological:	lack of neurologic symptoms
Skin:	clinical evidence of lack of allergic reactions
Musculoskeletel:	lack of arthritis or myalgias, normal values of CPK
Gastrointestinal:	clinical evidence of tolerability
Liver:	normal values of SGOT or SGPT, alkaline phosphatase, total bilirubin,
Kidney:	normal values of BUN or creatinine
Endocrine system and metabolism:	normal values of albumin or total protein, uric acid, glucose, cholesterol, amylase or lipase, sodium/potassium, calcium
Cardiovascular:	normal EKG and blood pressure
Haematopoietic:	normal values of complete blood count
Additionally:	more intensive investigation of any organ system likely to be particularly effected by the product

4.3. | Information needed to support phase 3 trials

- Safety data as in 4.2. If the population has broader entrance characteristics compared to the populations of prior trials, the favourable safety profile shown for constricted populations in prior trials may or may not convey to the broader populations in the phase 3 trials. Arguments that the product is likely to be safe in the broader population should be stated, and the phase 3 protocol should include re-testing of the safety parameters. Another reason to re-test safety parameters in phase 3 trials is the greater chance of identifying rare adverse events with the large number of patients used in phase 3.
- Preliminary efficacy data from phase 2 trials.
- Evidence from dose-ranging trials that the chosen dosing regimen is likely to be the optimum regimen with respect to safety and efficacy.

5. | ETHICAL CONSIDERATIONS IN CLINICAL TRIALS WITH HERBAL PRODUCTS

All of the fundamental ethical principles of human participation in research apply equally to herbal remedies and research involving these compounds. Consent must be obtained, subject selection must be equitable, risks and benefits must be weighed and must be favourable to the potential participant, and experimental design must be sound.

Concerns that particularly apply to clinical trials with herbal products include:

- Product adulteration (has it been documented?)
- Interactions between herbal remedies and other entities (rarely understood)
- Reproductive and organ toxicity data (may be minimal)
- Prior dose finding (likely to be incomplete).

The uncertainty in these areas must be clearly disclosed to all concerned, particularly during the informed consent process.

In many regions of the world, strong belief that herbal medicines will be beneficial and safe may introduce bias, which can be minimized by careful attention to study design including appropriate control groups.
Where possible, the community from whom the medicine originates should be consulted during the course of the research, and the results and benefits of the research should be shared with this community.

As in other types of research, a well trained, ethical investigator is the best assurance of patient safety in research. Therefore, skilled clinicians should be chosen as investigators to assure prompt recognition and appropriate treatment of any observed adverse event or worsening of a pre-existing condition.

Ethics committees must apply the same vigilant attitude towards herbal studies as they do towards conventional treatment protocols.

APPENDIX 1 | LIST OF CONTRIBUTORS TO THIS DOCUMENT

Dr Jonathan Berman (Chair), Director, Office of Clinical and Regulatory Affairs, National Center for Complementary and Alternative Medicine, 6707 Democracy Blvd, Suite 401, Bethesda MD 20892, USA. Tel: +1 301 594 7105; Fax: +1 301 480 3621; E-mail: bermanjo@mail.nih.gov

Dr Francis Crawley (Principal Rapporteur), European Forum for Good Clinical Practice, Schoolbergenstraat 47, B-3010 Kessel-Lo, Belgium. Tel: + 31 16 3503 69; Fax: + 31 16 350 369; E-mail: fpc@pandora.be

Dr Vasantha Muthuswamy (Associate Rapporteur), Senior Deputy Director General & Chief, Division of Basic Medical Sciences, Indian Council of Medical Research, Post Box 4911, Ansari Nagar, New Delhi 110 029, India. Telefax: +91 11 26589791(O), 23092868(R); E-mail: muthuswamyv@icmr.delhi.nic.in or vasanthamuthuswamy@yahoo.co.uk

Dr Angela Bowen, President, Western Institutional Review Board (WIRB), 3535 Seventh Avenue, SW, Olympia, Washington 985002, USA. Tel: +1 360 252 2440; Fax: +1 360 252 2490; E-mail: abowen@wirb.com

Dr Shaw Chen, Associate Director for Special Product Review - Botanical Drug and Medical Officer, DHHS/FDA/CDER/OND/ODEV, CRP2 Room 103, Rockville MD 20850, USA. Tel: +1 301 827 2601; Fax: +1 301 827 2317; E-mail: shaw.chen@fda.hhs.gov

Dr Vichai Chokevivat, Director General, Department for Development of Thai Traditional and Alternative Medicine, Ministry of Public Health, Tiwanond Road, Nonthaburi 11000, Thailand. Tel: +662 590 2603-4; Fax: +662. 590-2605; E-mail: vichai@health.moph.go.th

Prof Win Gutteridge, Consultant and Visiting Professor, LSHTM, 10 Soleoaks Drive, Sevenoaks, Kent, U.K. Tel: +44 1 732 454 923; E-mail: win.gutteridge@btopenworld.com

Dr Zhang Lei, Associate Professor and Head, Clinical Evaluation Group, Division of Traditional Medicine, Center for Drug Evaluation, State Food and Drug Administration, Jia-1 Fuxing Road, Beijing 100038, People's Republic of China. Tel: +8610-68585566-455; Mobile: 13911331089; E-mail: zhanglei37@sina.com

Ms Gugu Mahlangu, Director, Medicines Control Authority of Zimbabwe, P.O. Box UA 559, Union Avenue, Harare, Zimbabwe. Tel: 263 4 736981/5; Mobile 263 91 303 178; Fax: 263 4 736 980; E-mail: mcaz@africaonline.co.zw

Dr Jenny Mueller, Head, Clinical Research/Drug Safety Affairs, German Pharmaceutical Industry Association, Robert-Koch-Platz 4, 10115 Berlin, Germany. Tel: +49 30 279 09-1 14; Fax: +49 30 279 09- 3 14; E-mail: jmueller@bpi.de

WHO/TDR SECRETARIAT

Dr Juntra Karbwang, Clinical Coordinator, Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Geneva, Switzerland.Tel: +41 22 791 3867; Fax: +41 22 791 4774; E-mail: karbwangj@who.int

Dr Vladimir Lepakhin, Assistant Director-General, Health Technology and Pharmaceuticals, World Health Organization, Geneva, Switzerland. Tel: +41 22 791 4417/4804/4035; E-mail: lepakhinv@who.int

Dr Robert Ridley, Director, Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Geneva, Switzerland. Tel: +41 22 791 3803/3906; E-mail: ridleyr@who.int

APPENDIX 2 | GLOSSARY OF KEY TERMS

Herbal substance:
Material derived from the plant(s) by extraction, mechanical manipulation, or some other process.

Herbal product:
The herbal material administered to clinical subjects.

Herbal product synonyms:
Herbal remedy, herbal medicine, herbal drug, botanical drug.

Active pharmaceutical ingredient (API):
The chemical constituent that accounts for the efficacy or other therapeutic effect of the herbal substance or herbal product.

Chemistry-manufacturing-control (CMC):
The chemical and manufacturing processes, and the control of these processes, that are used to create the herbal substance and the herbal product.

Good Manufacturing Practices (GMP):
A set of standards that ensures that CMC procedures are performed as well as possible.

Good Clinical Practices (GCP):
A set of standards that ensures that clinical procedures are performed as well as possible.

Comments and suggestions on all aspects of this Operational Guidance are welcome for consideration in future revisions.
Please correspond with:

Dr Juntra Karbwang
Clinical Coordinator
Special Programme for Research and Training
in Tropical Diseases (TDR)
World Health Organization
CH-1211 Geneva 27
Switzerland

Tel: +41 22 791-3867 (8)
Fax: +41 22 791-4774
E-mail: karbwangj@who.int
Website: www.who.int/tdr

Mailing address:
TDR
World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland

Street address:
TDR
Centre Casai
53, Avenue Louis-Casai
1216 Geneva
Switzerland

Tel: (+41) 22-791-3725
Fax: (+41) 22-791-4854
E-mail: tdr@who.int
Web: www.who.int/tdr