CLINICAL TRIALS OF HERBAL MEDICINES

Herbal medicines include a wide range of products that spans from plants collected by people themselves to medicinal products extracted and purified from botanical sources. Many herbal medicines lack acceptable data on efficacy, safety, quality control, standardization and differentiation of indication (i.e. preventive, prophylactic, and curative). Herbal medicines have constituents with variable mechanisms of action that modify physiological functions. Variability could be due to type of soil, harvest time, preparation (i.e. drying, storage, solvents, mode of extraction, manufacturing process etc.) Few of them have become available through the traditional phase l-lll clinical trial testing and sometimes the dose-response relationship is not clear. Agents are used individually or mixed with other herbs in a tea although some may be also administered orally (pills, capsules or elixirs) parenteral (SC or IV), or via enemas. Herbal medicines are considered safer than conventional medicines and allegedly have fewer side effects than synthetics. [Tamayo, 1999]

Herbal medicines are often used in a different context than conventional medicine and are used as symbols for natural, healing, harmless, supportive, integrative etc. Claims for herbal medicines offer hope and a promise to extend life expectancy and improve quality of life and despite the evidence are presented to consumers as medicines. Herbal medicines can also have adverse effects and can interact adversely with other herbs and drugs.

Consumers, clinicians, and corporations are taking an interest in botanical medicine. In third world countries, herbs are widely used by traditional healers. In industrialized countries, herbals and dietary supplements are an important market. Some countries like Germany have a long tradition in the use of herbal preparations marketed as drugs. In the US and UK herbal medicinal products are marketed as "food supplements" or "botanical medicines" [Linde, 2001].

Considering the widespread use and popularity of herbal products the need for adequate evidence on the effectiveness and safety of herbals is mandatory. Clinical evaluation of herbal medicines is an ongoing process and should include adequate knowledge and understanding of values and limitations of clinical research, particularly randomized controlled clinical trials.

1. BASIC CONCEPTS

Clinical Trial

A clinical trial is a type of research study that answers specific questions about new (and old) therapies or interventions. Clinical Trials are used to determine whether new drugs or treatments are, both safe and effective [NIH, 2001] and whether new therapies offer advantages over existing "standard" therapies.

Randomized Controlled Trial

The randomized controlled trial (RCT) is a research tool, and it has been defined as one of the "simplest, most powerful and revolutionary" [Jadad, 1998a]. An RCT seeks to measure and compare the outcomes of two or more clinical interventions. In essence, RCTs are quantitative, comparative, controlled experiments in which a group of investigators studies two or more interventions in a series of individuals who receive them in random order [Jadad, 1998b, Altman, 1991].

RCTs are planned experiments because the investigators can influence the number and the type of interventions, as well as the regimen (amount, route and frequency) with which the interventions are applied to the participants. RCTs are different from observational studies (where all the events are measured but not influenced by the investigators and the interventions are not randomly assigned). Observational studies can be controlled or non-controlled and, depending on how the data are gathered in time, they can be prospective, retrospective, or cross sectional (at a specific point in time). Characteristics and methodology of the different types of observational and non-randomized studies have been published elsewhere [D'Agostino, 1995, Fletcher, 1996].\

CLASSIFICATION OF RCTs

RCTs can be classified according to: (1) the aspect of the interventions, investigators want to explore; (2) the way in which the participants are exposed to the interventions; (3) the number of participants

included in the study; (4) whether the investigators and participants know which intervention is being assessed; and (5) whether the preferences of non-randomized individuals and participants are taken into account [Jadad 1998a]. The most common types of RCTs according to the aspect of the interventions investigators want to explore are:

Pragmatic trials
Trials designed to determine whether the intervention works, but also to describe all the consequences of its use, good and bad, under circumstances mimicking clinical practice [Sacket, 1979].

Explanatory trials
Trials designed to establish efficacy (also called efficacy trials), they are designed to yield a 'clean' evaluation of the effects of the intervention. The investigators are interested in including participants who will follow their instructions and who will receive the intervention and are not so interested in finding out how the intervention works [Jadad, 1998a].

Phase I trials (Drug Safety)
These are the first studies conducted in humans to evaluate a new drug. Phase I trials assess the safety of agents never before administered to humans. These trials are intended to establish a safe dose for a new drug, determine the sites, extent and duration of toxicities and look for therapeutic effects [Jadad, 1998a]. Phase I trials are conducted once the safety and potential efficacy of the new drug have been documented in animals. They are used to establish how much of a new drug can be given to humans without causing serious adverse effects. In other words, the goals of phase I trials are to determine the relationship between toxicity and dose-schedule of treatment for a given drug, and to understand how the drug is distributed, stored, excreted and utilized in the body (pharmacokinetics and metabolism) and it's biochemical and physiological effect (mechanism of action and pharmacodynamics). These trials aim to answer the question: How much drug can be given without causing serious side effects?

Phase II trials (Initial treatment effect)
These trials are intended to determine activity of a new agent and whether further trials are justified [Wittes, 1985]. In these trials, the new drug is given to small groups of patients with a given condition (usually about 20 per trial). The aim of phase II trials is to establish the efficacy of different doses and frequencies of administration but no comparisons are made with other interventions. Even though phase II trials focus on efficacy, they can also provide additional information on the safety of the new drug. [Jadad, 1998a; Green, 1992]. Outcomes are usually focused on short-term physiological responses (e.g. tumor response in cancer trials). Often, phase II trials are not randomized, particularly when the therapeutic effects of the new drug can be measured objectively. These trials aim to answer the question: What is the "cure rate" of this disease with this drug?

Phase III trials (Full scale evaluation)
These trials are designed and conducted once a new drug has been shown to be reasonably effective and safe in phase II trials. Phase III trials are typically effectiveness trials, because they seek to compare the new drug with an existing drug or intervention known to be effective. This existing drug is usually regarded as the current standard treatment [Pocock, 1983]. In phase III trials everything needs to be defined in terms of "measurable" quantities and often have multiple endpoints. They are designed to minimize erroneous conclusion by balancing characteristics affecting prognosis and minimizing all potential sources of bias. This requires prospective randomization of treatment assignment, sufficiently large numbers of patients in each arm and stratification or characteristics known to influence response to therapy and natural history of the disease [Kauffman, 1994]. Most phase III trials are RCTs. These trials aim to answer the question; Is the new treatment better than the standard?

Phase IV trials (Post marketing surveillance)
The term 'phase IV trial' is used to represent large studies that seek to monitor adverse effects of a new

drug after it has been approved for marketing [Armitage, 1994]. It also refers to long-term studies of morbidity and mortality. They are mostly surveys and seldom include comparisons among interventions. Phase IV trials are not RCTs.

2. RCTs METHODOLOGY CONCEPTS

Bias
Bias is any factor or process that tends to deviate the results or conclusions of a trial systematically away from the truth [Sackett, 1979b]. For example, bias could occur when the dose of the conventional therapy is too low to be effective, increasing the probability of benefit associated with a new treatment, not measuring what you want to measure. This deviation from the truth can result in underestimation or exaggeration of the effects of an intervention. Bias can occur in a trial during the planning stages, the selection of participants, the administration of interventions, the measurement of outcomes, the analysis of data, the interpretation and reporting of results, and the publication of reports [Jadad, 1998a],

Blinding
Masking or blinding means that subjects are unaware of which treatment they are receiving. it represents any attempt made by the investigators to keep one or more of the people involved in the trial (that is, the participant or the investigator) unaware of the intervention that is being given or evaluated. The purpose of blinding is to reduce the risk of ascertainment or observation bias. This bias is present when the assessment of the outcomes of an intervention is influenced systematically by knowledge of which intervention a participant is receiving. Blinding can be implemented at least at six different levels in an RCT. These levels include the participants, the investigators or clinicians who administer the interventions, the investigators or clinicians who take care of the participants during the trial, the investigators who assess the outcomes of the interventions, the data analysts, and the investigators who write the results of the trial [Jadad, 1996; Jadad, 1998a,]. Therefore, depending on the extent of blinding, RCTs can be classified as open, single-blind, double-blind, triple-blind, and quadruple-blind.

Compliance
It is the extent to which study participants follow the instructions and receive the intervention given by the investigators. It usually refers to the doctor's instructions for taking medicines or filling out questionnaires. In general medical practice compliance implies following doctor's directions as part of the prevention or treatment of a disease. Compliance is also known as adherence.

Control group
Is the standard by which experimental observations are evaluated. It is also called comparison group and refers to the group of participants who receive conventional practice, a placebo, or no intervention at all. Sometimes the control can be the best available intervention.

Effectiveness
Effectiveness refers to whether an intervention works in people to whom it has been offered. Effectiveness is usually determined with "effectiveness trials". Effectiveness trials evaluate interventions with proven efficacy when they are offered to a heterogeneous group of people similar to those seen by clinicians in their daily practice.

Efficacy
Efficacy refers to whether an intervention works in people who receive it. Efficacy is determined by explanatory trials.

Placebo
Placebos are 'fake' substances or actions that can cause an effect on people who take them believing that they are real [Jadad, 1998], Placebos are used to make attitudes in both treatment groups as similar as possible (same schedule, same looking medication).
Placebos are frequently used in clinical trials to evaluate whether any improvement or adverse effects from a new treatment are 'real'. Placebos have been traditionally regarded as deceptive therapies and have not been- understood in the broader context of social symbols and of interpersonal factors that surround the healing process itself. Although the power of inert substances to heal is well recognized, the placebo effect also influences the outcome of conventional therapies. Few studies are designed to measure the placebo response rate directly. However, a recent review on-the effect of placebo as a treatment found that there is little evidence that placebos had powerful clinical effects and that that they may not be better than groups with no treatment. The authors concluded that "placebos had a small beneficial effect in studies with continue subjective outcomes but outside the setting of clinical trials there is no justification for the use of placebos" [Hrobjartsson, 2001]. In any case, placebos are a reminder of how little is known about mind-body interaction and in general, the placebo effect may be one of the most versatile and underused therapeutic tools at the disposal of physicians [Margo, 1999].

Randomization
Participants receive the interventions in random order to ensure and unbiased assignment to treatment by removing any differences between the groups. Similarity of characteristics at the start of the comparison can be achieved through a variety of procedures: Individuals, groups, and the order in which measurements are obtained can all be randomized [Altman, 1991]. Randomization balances known and unknown prognostic factors between the groups as it reduces biases in the comparison of the treatment and control by making people equal with respect to all features except the treatment assignment [D'Agostino, 1995].

Random sample
Random sample is a set of items that have been drawn from a population in such a way that each time an item is selected; every item in the population has an equal opportunity to appear in the sample [Hoffman, 2000].

Statistical significance
A finding (for example the observed difference between the means of two random samples) is described as statistically significant, when it can be demonstrated that the probability of obtaining such a difference by chance only, is relatively low [Hoffman, 2000]. Clinical significance is slightly different and is related to determining the smallest difference between two treatments that is clinically important to detect.

3. HERBAL MEDICINE CONCEPTS

Herbs
Plants or plants products that contain chemicals, that act upon the body. [NC-CAM, 2001]

Herbal Medicines/Phytomedicines
Preparations derived from plants or fungi believed to have healing qualities. They are usually prepared by alcoholic extraction or decoction. Herbal medicines may be useful to prevent and treat diseases and ailments or to promote health and healing. Many conventional drugs originate from plant sources and some of the most effective drugs currently used in medicine are plant based. Examples include aspirin (from willow bark), digoxin (from foxglove), quinine (from cinchona bark), morphine (from the opium poppy), reserpine (from snakeroot), vincristine (from Magadascar periwinkle) and taxol (from Pacific yew). Herbal Medicines are widely used by traditional medical systems such as traditional oriental medicine (Chinese Medicine), India's traditional system of medicine (Ayurved Medicine) and many Native American, Aboriginal, African, Middle-Eastern, Central and South American cultures.

Herbal medicines are used in two different ways: (1) to treat symptoms and diseases, comparable with other drug therapies in a patient oriented setting (e.g. according to the individual physical and mental constitution of a patient) and (2) to help the patient to overcome the causes of disease or to strengthen their defense system (prophylaxis).

Herbal drugs
These are a mixture of chemical compounds derived from plants and usually have one active substance whether or not the constituents with therapeutic activity or active principle are known. Herbal drugs can possess significant pharmacological activity and consequently, potential adverse effects and drug interactions.

Herbalism
The practice of herbal medicine by individuals using principles such as combining herbs and unconventional diagnosis that tends to concentrate on treating chronic conditions. The aim of herbal treatment is usually to produce persisting improvements in well-being. Modern Western herbalism emphasizes the effects of herbs on individual 'body systems.

Nutraceutical
This is a word that was created by combining the words Nutrition and Pharmaceuticals, creating the concept' that extracts from food can be used as drugs, i.e. food or dietary supplements. Nutraceuticals (often referred to as phytochemicals or functional foods) are natural, bioactive chemical compounds that have health promoting, disease preventing or medicinal properties. Phytochemical is a chemical dietary supplement that comes from plants (e.g. isoflavones from soy, antioxidants from vegetables, lycopene from tomatoes [Hoover, 2000].

4. HERBAL MEDICINE RESEARCH METHODOLOGY

Health benefit
A benefit from a nutraceutical that prevents or reduces the risk of a disease or health condition, including the management of a disease or health condition, or improves health and well-being. (Nutraceutical Research and Education Act, USA).

Health Claim
Health claims are among the various types of claims allowed in food labeling. They show a relationship between a nutrient or other substances in a food and a disease or health-related condition. They can be used on conventional foods or dietary supplements [FDA 1998, FDA 2001].

Safety
It refers to side or adverse effects of an intervention. Herbal medicines are generally considered safe compared to conventional drugs. While this is probably correct case reports show that severe side effects and relevant interactions with other drugs can occur. Several reviews summarizing herb's side effects and interactions have been published [Fugh Berman, 1999, 2000; Ernst, 2000a, 2000b]. Many plants are highly toxic and herbal products may be contaminated, adulterated, or misidentified and probably presents a greater risk of adverse effects and interactions than any other complementary therapy [De Smet, 1995].

Standardization
It refers as to whether different products, extracts, or even different lots of the same extract are comparable and equivalent. For example, Echinacea products can contain other plant extracts, use different plant species *(E. purpurea, pa/lida* or *angustifolia),* different parts (herb, root, both), and might have been produced in quite different manners (hydro or lipophilic extraction) [Vickers 1999, Vickers 2001, Linde, 2001J.

Quality of Herbal Medicinal Products

Consistent quality for herbal medicinal products can be assured only if the starting materials are defined in a rigorous and detailed manner, which is usually done with the help of a pharmacopoeia monograph. Regarding the total extractable matter and if applicable, the active principle, requirements made in the pharmacopoeia must be met or minimum contents and/or ranges must be defined. In order to maintain the consistent quality of medicinal products of plant origin, it may also become necessary to use herbal drugs from various harvests and/or sites of collection. Quality assurance should not mean standardization according to single compounds, if the active ingredients are not definitely known, but quality of manufacturing. For herbal drugs, which have a long tradition in the Western Hemisphere, experts in this field should create herbal monographs. Reproducible data is necessary if heterogeneous botanicals are to be labeled as medicines.

5. ISSUES IN CLINICAL RESEARCH OF HERBAL MEDICINES

Although large gaps remain in research, many clinical trials of herbs exist [Fugh Berman, 1997]. Thirty out of seventy nine potentially relevant reviews evaluated Ginkgo (for dementia, intermittent claudication, tinnitus, and macular degeneration), Hypericum (for depression) or garlic preparations (for cardiovascular risk factors and lower limb atherosclerosis). The review also found that there is very little evidence on the effectiveness of herbalism as practiced by specialist herbalists who combine herbs and use unconventional diagnosis [Linde, 2001J. In addition, the number of MEDLINE Indexed CAM publications has increased significantly from 1987 through 1996, reaching around 10% of the total in 1996 [Barnes, 1999], the Cochrane Library now includes nearly 50 systematic reviews of complementary medicine [Ezzo, 1998]. The number of randomized CAM clinical trials has approximately doubled since 1996 [Vickers, 1998]. The majority of CAM **RCTs** have been conducted in herbal medicines.

Methodological Issues

In evaluating herbal medicines a variety of different research designs need to be used to answer the different questions relevant to herbal products: from clinical research on therapeutic efficacy to basic science research on mechanisms of action and pathogenesis [Levin, 1997].

The value of observational studies should not be underestimated. Uncontrolled trials and observational studies can facilitate CAM research and inform the design of intervention trials. Observational studies can help to establish that a clinical effect is worth investigating, identify the most suitable patients and the most appropriate treatments, and provide information on how large the effect might be [Gill, 1996]. Well-conducted and reliable complementary and alternative medicine research poses issues for the overall delivery of contemporary health care.

More collaboration is needed to overcome the limitations of conventional research in the evaluation of herbal therapies in particular. Nevertheless, appropriate methodologies can normally be found in one or another of the diverse branches of medical research around herbal products [Vickers 1996]. Within conventional research methodology (quantitative and qualitative) it is possible to find many rigorous tools such as the RCT to evaluate the efficacy and safety of interventions. In fact, innovative or "alternative" methodologies may be necessary only in isolated circumstances. Data-analytic procedures (i.e., analysis of variance, logistic regression, multivariate modeling techniques) are quite satisfactory for addressing the majority of study questions related to CAM particularly those on therapeutic efficacy of herbal medicines because it is often possible to test a single agent just as one would evaluate any other pharmaceutical product.

RCTs Issues

We must consider that the undertaking of an RCT does not guarantee valid results, and the findings of RCTs of,the same intervention are often discrepant [Jadad, 1998b]. RCTs can help to show what is useful but not always show what is true [Armitage, 1998]. it is important to reiterate that although RCTs can tell us which treatment is generally better, even when they have been perfectly executed they cannot tell for which specific individuals a treatment is better and this may limit their application in CAM research.

The more accurate the randomized trial is, the less its results can be generalized, and some authors even argue if generalization on the basis of RCTs is ever feasible. Researchers should understand the limitations of RCTs, feel comfortable with the fact that there are many situations in which RCTs are not feasible or appropriate and that multi-patient, double-blind, randomized controlled trials have not or cannot be carried out. It is well known for example, that only 40% of interventions used in pediatric medicine have been evaluated using RCTs [Rudolf, 1999] that means that 60% have not been completely evaluated yet still widely used. Similar results have been published about psychiatric interventions [Geddes, 1996],
Limitations, value and challenges of RCTs have been reviewed elsewhere [Chalmers, 1983, Kramer, 1984, Detsky, 1989, Hellman, 1991, Wittes, 1994, Jadad, 1996, 1998b] and several authors have addressed the usefulness and limitations of different types of RCTs both in conventional medicine [Leventhal, 1988, Gould, 1991, Bottomley, 1997, Hermann, 1998, Resch, 1998, Wilson, 1998, Abel,^ 1999, Britton, 1999, Vijan, 2000], particularly in psychosocial research [Clarke, 1995, Hotopf, 1999, Wells, 1999] and in CAM [Vickers, 1996, Hilsden, 1998, Jacobson, 1998, Walker, 1999]. During the past 10 years RCTs have become the subject of research rather than the tool of research [Jadad, 1998a] and several lessons have been learned (See Annex 1). These lessons may be the initial issues any researcher should consider when considering the evaluation of herbal medicines using RCTs.

6. GOOD PROTOCOL CHARACTERISTICS

First of all any clinical research should be always motivated by two definite laws: "Do No Harm" or the obligation to secure the well being of individual and "Do Good" or to enhance the ability to secure the well-being of individuals in the future [Des Jardins, 2000]. In addition we always should keep in mind that clinical studies should satisfy the needs of those who are trying to make decision in the front line: patients and health care professionals [Bero,' 1997]. A good clinical protocol should describe types of people *who* may participate in the trial, the schedule of tests, procedures, medications and dosages; and the length of the study. A comprehensive protocol of a clinical trial in herbal medicine should also consider the following aspects:

Label Driven
How much evidence and what type of evidence would you need to put claims in a label? Some said that the evidence should not differ from that needed for conventional products. Others said that there are differences and the level of evidence should differ. People argue that herbal medicine is different, that herbs are inherently safer; most herbs has a long historical record of use by thousands of individuals and there is no reason of testing isolated chemical components of a particular plant when there may be a synergistic effect of components [Tamayo, 1999]. In the case of traditional herbal systems that involve complex therapies and multiple interventions, it may not possible to do specify specific claims.

Patient selection
Each protocol should specify criteria for patient eligibility. The number of patients should be sufficient to meet the study objectives. Definite comprehensive eligibility and exclusion criteria must be clearly stated. These criteria will often encompass factors such as the precise extent of disease spread, histologic and other diagnostic measures, the extent of prior therapy, organ sufficiency determined by specific laboratory parameters, co-morbidity and possibly a variety of other restrictions such as age, gender, anticipated compliance problems, history of smoking and alcohol intake, etc. When selecting patients one should consider that human beings are highly variable in their response to treatment. Too much variability in the outcome measure will lead to a negative result. Variance may be decreased by exclusion criteria (only those with "severe disease, old age or young age, etc.). However, decreasing variance may risk validity and applicability of the results. Another issue to consider that may affect patient selection is the setting where the study is going to be conducted. Usually herbal preparations are used by ambulatory patients so it may be advisable to conduct trials in outpatients clinics instead of hospitals for example.

Accurate/Reliable/Relevant Data
Regarding administration: Optimize dose selection and route of administration.
Measurement frequency and timing of administration: how and when the herbal product is going to be administered.
Regarding dosage: Standardization and concentration of the herb should be pre-determined and specified as well as presentation of the product (pill, vial, tea, etc)
Regarding safety. How reliable is the historical data? Are there any data on toxicological studies in animals and humans?
Regarding the Patient/Subject: Disease Characteristics, health condition of the patient.

Informed Consent
The Informed Consent is a document containing information about the study that should be presented to all participants. It assures that the patient understands the research in which he/she is participating. An informed consent should be non-threatening, freely obtained, written and non-coercive and interventions should be described simply and factually. Aims and methods of the study, potential hazards and benefits should be stated. Respect for privacy and confidentiality. Subject can withdraw at any time without interfering with the doctor/patient relationship.

7. CLINICAL TRIAL DEVELOPMENT

RCTs are required for the unequivocal demonstration of the efficacy of a treatment. Evidence from at least two positive well-designed and conducted placebo-controlled studies is generally accepted as appropriate to establish the efficacy of a drug [Gould, 1991].
There are several stages in preparing clinical research studies. Stage 1 includes identifying the purpose of the inquiry and finding the essential financial resources. Careful thinking about the clinical practice to be investigated and the allocation of time for research is also necessary. Stage 2 involves assessing the feasibility of the study. Statistical decisions are best made before data are collected, and this means consultation with a statistician or methodologist. There has to be ethical approval from the cooperating institution. A thorough search of the literature is fundamental. In Stage 3, the final trial is designed, ethical approval obtained, and the proposal is submitted for funding. In the final stage, Stage 4, the trial is carried out, analyzed, and prepared for publication [Silverman, 1996].
Reports of RCTs should provide readers with adequate information about what went on the design, execution, analysis and interpretation of the trial. Reports should help readers judge the validity of the trial and discussions about the implications of the study should be limited. Guidelines for the reporting of clinical trials are available in the literature [Green, 1988; Begg, 1996]
Considering that much more alternatives exist than one would imagine in terms of selection and designing of clinical trials, there are some rules that need to be followed for an adequate conduction of a clinical trial. In herbal medicine evaluation one should consider the different paradigms.

8. Clinical Trials Designs to Evaluate Herbal Medicines
As previously mentioned the design of clinical trials depends on the research question. In pragmatic trials the research question is: 'How do I treat patients with this disease?' In explanatory trials this question is: 'What is the mechanism of this new treatment?' In order to conduct adequate clinical trials of any CAM therapy but particularly herbal therapies the well-informed and motivated physician should be part of a team that should include herbalists, herbal practitioners, clinical epidemiologists, statisticians, nurses and technicians. If trials are to be used efficiently, and if evidence based decision making is to reach its full potential, we will need to couple our efforts to increase the understanding of RCTs with efforts to promote a better understanding of the relationship between RCTs and other study designs, between research information of all kinds and other types of information, and between information available to decision makers, their values and preferences, and the circumstances in which they are making the decisions [Jadad, 1998b].

Before deciding to embark in an RCT, especially in an RCT of an herbal therapy, one must ask: Is the trial important? Will a demonstration of statistically significant superiority of one therapy over another make a meaningful difference in clinical practice or in patient outcome? One should hope that a proposed RCT would meet the Gertrude Stein test: A difference is not a difference unless it makes a difference [Kaufmann, 1994, Stein, 1990], Different types of designs proposed in the evaluation of other conventional therapies [Zelen, 1979, Gould, 1991, Ernst, 1995, Chadwick, 1997] might also be appropriate for the evaluation of herbal medicines and should be considered whenever possible. A complete analysis of the different types of clinical trials that can be used in the evaluation of herbal medicines is out of the scope of this chapter but there are some designs that might be considered such as:

Pragmatic Trials

Because pragmatic trials can be designed to take patient preferences into account and does not necessarily require that the patient or the therapist is 'blind' to the treatment being given this may be a good design to test herbal medicines. In these trials, generalizability of the results is very important and so the trial participants should resemble, as far as possible, the future patients to which the best treatment will be applied. In addition, outcomes measures can be based on selected groups.

Pragmatic trials are characterized by liberal patient selection, open treatment modalities corresponding with regular care, outcome measures considered from the patient's perspective and intention-to-treat analysis. To achieve this, pragmatic studies tend to use more lax criteria include flexible regimens, include participants with heterogeneous characteristics and allow them to accept or reject the interventions offered to them and include and analysis of the patients who received the interventions. In this type of trials accrual is not a major concern due to the fact that patient heterogeneity can be assessed and adjusted for in the analysis [Feinstein, 1985].

Equivalence Trial

Trials designed to show that the interventions are, within certain narrow limits, 'equally effective' [Armitage, 1994] or equally efficacious. Often, these trials seek to demonstrate that a new intervention (or a more conservative one) is at least as good as the conventional standard treatment [Jadad, 1998b, Gould, 1991]. Investigators who engage in equivalence trials make efforts to minimize the risk of suggesting that the interventions have equivalent effects when in fact they do not. This design may be very useful in the evaluation of herbal medicines with well-known clinical activity but that may be cheaper and safer than conventional treatments.

Comprehensive cohort design

In these trials participants are followed up, regardless of their randomization status, if a person agrees to take part in an RCT, he or she is randomized to one of the study interventions. If the person does not agree to be randomized because he or she has a strong preference for one of the interventions, that person will be given the preferred intervention and followed up as if he or she were part of a cohort study [Olshewsky, 1985, Brewin, 1989]. At the end, the outcomes of people who participated in the RCT can be compared with those who participated in the cohort studies to assess their similarities and differences.

This type of design is ideal for trials in which a large proportion of eligible individuals are likely to refuse to be randomized because they (or their clinicians) have a strong preference for one of the study interventions (most likely to be an herbal medicine). One of the main limitations of this type of design is that any differences in outcomes may be explained by differences in the baseline characteristics of the participants in the randomized and non-randomized groups [Torgerson, 1996]. It will be important in this case to select homogenous populations in the different groups involved.

Optional Cross-Over Design

This design is good in situations where not "hard" endpoints can be identified or measured [Ernst, 1995]. This may be appropriate in the evaluation of holistic herbal therapies where the complex and subjective experiences of patients need to be evaluated. In this RCT two treatment groups (A and B) receive the randomly allocated active treatment or placebo for a pre-determined period of time (phase I of the trial).

At the end of phase I the patient reports the effect of the treatment and the patient along with his/her doctor makes a decision to change the treatment received and phase II begins. During phase II, treatments (placebo or active medication) are as in phase I except for those patients who have chosen to crossover. In this way both groups A and B have a chance of treatment with the active medication.

Partially Randomized Patient Preference Design (Wennberg's design)
In these trials eligible individuals are randomized to a 'preference group' or an 'RCT group.' Those individuals in the preference group are given the opportunity to- receive the intervention that they choose among several options offered, whereas those in the RCT group are allocated randomly to receive any of the study interventions, regardless of their preference. At the end of the study, the outcomes associated with each of the interventions in each of the groups are compared and used to estimate the impact of the participants' preferences on the outcomes.

N of 1 Trials
This design may be an appropriate method to test highly individualized therapies. Methodology to conduct this type of trials has been published in the literature [Guyatt, 1986, 1988; Sackett, 1991, Vook, 1996]. This type of trials are designed to evaluate therapeutic preferences in patients with chronic stable conditions and are useful to evaluate treatments that has rapid onset of action and ceases to act soon after it is discontinued.

Phase I Trials
May be conducted when there is clear evidence that a particular herbal preparation has specific clinical activity. In this case motivation to do a phase 1 clinical trial of an herb may be solely academic and may come after the herbal preparation have been tested in efficacy trials.
Phase II Trials
May be conducted in the evaluation of new potentially effective herbal therapies that have not been previously evaluated to determine clinical activity. The usual approach is to conduct a "pilot phase l/ll" clinical trial particularly if there is no previous data about the administration, dosage and safety of the herbal preparation.
Phase IV Trials
Although not RCTs these trials may be appropriate to evaluate patients using well-known, widely available herbal products. Strategies to conduct this type of the studies using patient-self monitoring systems have been described [Fisher 1992]. This strategy might be useful in phase IV studies of herbal products.

Quasi-Experimental and Non-Experimental (Observational) Study Designs
These are other designs that might be considered when evaluating herbal medicines. As stated before, alternatives to RCTs are available and should be considered whenever possible.
Recent studies have suggested that observational studies can be sufficiently well designed to yield data comparable to those of some RCT [Concato, 2000; Benson, 2000, Pocock, 2000]. It had been claimed that observational studies find stronger treatment effects than randomized controlled clinical trials and the potential of bias due to the presence of confounding factors is greater that in randomized, controlled studies. This fact has prevented the use of-'this type of studies, in the evaluation of treatment effects. However, a recent systematic review reports that there is little evidence that estimates of treatment effects are either "consistently larger or qualitatively different from those obtained in RCTs". In addition, the authors conclude that observational studies do provide valid information [Benson, 2000]. Therefore, well-conducted observational studies may be useful in the evaluation of herbal therapies.

Prospective Cohort Studies
In this type of study, groups are formed in a non-random manner according to levels of hypothesized cause that may be different treatments (referred as the independent variable) and subsequently observed with respect to the outcomes of interest (referred to as the dependent variable). These studies may help

to* determine a relationship between the purported cause and effect and useful in assessing multiple effects of a given exposure.

Clinical Series

A clinical series is a record of clinical experience. It is often an inexpensive method and can take the form of a single case report or a series of consecutive cases [Moses, 1992]. It can be used to report the application of a new technique, how to apply it and difficulties and complications of its application. These type of studies are inadequate to determine effectiveness of the intervention but can be useful in assessing new treatments by comparing the whole series with conventional expectations and experience.
Well-conducted case series may be feasible to do in a majority of clinical practices where herbal medicines are used. However, analysis of retrospective data in patients who have used a variety of herbal preparations during long periods of time may be cumbersome. Series may differ in the definition of objectives and patient eligibility and matching is hard to accomplish. In addition validity of diagnosis, health status of patients, co morbidity and other therapeutic interventions may be difficult to obtain for a "good case series" to be assembled.

POMES

Special attention must be given to the Prospective Outcome Monitoring System (POMES) design proposed by the National Center for Complementary and Alternative Medicine (NC-CAM) in the United States in 1997. Although not an RCT the POMES may facilitate the evaluation of herbal therapies particularly those used within traditional medical system or a part of the integrative approach that many CAM practitioners use in their regular practice. Originally created to evaluate alternative cancer therapies POMES may be applicable to other therapies as well. Information about principles and methodology of POMES have been developed and are available at the NC-CAM web page [NC-CAM 2001 b]. Practice-based clinical trials are carried out to evaluate CAM practices that utilize complicated, individualized approaches to manage patients. The system emphasizes excellent record keeping and rigorous patient follow-up through the conduction of a prospective, practice based, single-armed outcome study.

9. CHALLENGES OF HERBAL MEDICINE'S RCTS

Investigation of CAM interventions, particularly herbal medicines using randomized controlled trials is possible [Margolin, 1998]. However, depending on the intervention, it can be associated with a number of challenges, most of which are shared by research on conventional pharmacological therapies. Early identification of these challenges is necessary so that the research team has adequate time to plan strategies for overcoming them.
These challenges include: design issues (eg. identification of clinically relevant research questions, selection of interventions and controls, standardization of interventions, blinding, and placebos); recruitment issues (including randomization and compliance issues), analysis issues and ethical issues. In herbal medicine research the most common challenges that the investigator may encounter are:

Design Issues

Identification of research questions

The question being asked is what should determine the study design that can best answer it [Sackett, 1997]. Differentiation between "does it work" and "how it works" should be done at the beginning of any project. In herbal medicine safety and efficacy are key issues but they can be addressed in different ways. The basic questions need to be related to the definition of the disease (what?); the definition of treatment (How many? When to treat? How chosen?) and the definition of outcomes (How do we follow? How long? What do we measure?)

Selection of interventions and controls:

This may be one of the major challenges in the clinical evaluation of herbal therapies. Adequate choice of comparators or control interventions may be difficult for herbal medicines that have well known medical effect but the mechanism of action is not known. Strategies should be developed to minimize the participation of individuals with clear conflicts of interest in the design, execution, and reporting of

clinical trials and alternative designs to placebo-controlled studies can be considered. For example, the conventional approach in clinical trial is "bench to bedside", that is we find a chemical compound, test it in the laboratory, then in animals and eventually we conduct RCTs of that product. However, the approach to CAM research is often the exact reverse: 'bedside to bench' [Boon, 2001, Tamayo, 2001]. Consumers are already using CAM and they are not interested in what the product does in mice, not interested in how it works or why it works. So CAM researchers may initiate clinical trials of products without much data on the actual product, mechanism of action or adverse effects.

It is important to design the active and control treatments to be equivalently credible and to assess the credibility' of the treatments. One way to accomplish this is through multiple administrations of treatment credibility assessment instruments, which permits for comparisons across groups of patient-perceived credibility of the assigned treatment [Borkovec, 1972, Vincent, 1990, Meinert, 2001], Other factors also add to the challenges faced by CAM researchers in the selection of controls. For example, some CAM cannot be evaluated by reductionist methods: testing isolated chemical components derived from a particular plant is often not helpful in identifying its clinical effects because patients ingest the plant as a whole and proponents of herbal medicine believe that many of the effects are the result of the synergy of the multitude of compounds present in the whole plant material. Evaluation of CAM should also consider the different paradigms on which specific products and therapies are used. For example: Ayurvedic medicine often uses a combination of products; not only an isolated herb and doing clinical trials of paradigms are a challenge.

Standardization of the intervention

On the health food store shelf the high quality, standardized products used in the trials might not be available. Herbalists and herbal medicine practitioners should be included in the design and execution of the trial. Most of the time, only an herbal medicine expert can judge with some certainty whether the product you are using is the right one and whether the results can be extrapolated to the product of interest. It can be very difficult to standardize dietary supplements that are composed of many different herbs on which the active components are not yet identified.

Standardization is a requirement of the major funding agencies in the world. The National Institutes of Health (NIH) in the United States for example, does not provide funding if the product is not standardized and the sources are not reliable. NIH currently requires that all dietary supplements, nutraceuticals and herbal medicines used in clinical trials be standardized to contain known contents.

Placebo

For dietary supplements and herbal medicines that are ingested in pill form is not fundamentally different from creating placebos for other pharmaceutical product. However, finding an inert placebo that looks, smells and tastes like an herbal mixture that is normally mixed with water to create an herbal "shake" can be a great challenge [Tamayo, 2001]

Recruitment Issues

It can be difficult to enroll patients in trials of herbal medicines or dietary supplements that are commercially available. Rather than the "risk" of being randomized to a placebo group, patients that believe the product may help them are likely to simply purchase the product. One way to overcome this challenge is to provide the "real" product free of charge at the end of the study to participants who were randomized to receive the placebo [Tamayo, 2001]. Barriers to participation in CAM clinical trials includes difficulties in recruiting, randomizing and retaining patients in clinical trials particularly those patients who "believe" CAM therapies are effective are a major challenge. The number and type of patients accrued to clinical trials is determined by the eligibility criteria stated in the protocol. In addition, younger, well-educated patients are the usual consumers of herbal medicines; this may be an issue to consider when you are interested in evaluating herbal therapies in older patients.

Randomization

It has been consistently demonstrated that among patients eligible for protocols the primary motivation for non-participation was a physician preference for a particular therapy or alternative treatment. That is, physician reticence about randomization or possible about having to deal with informed consent. [Begg CB, 1988]. This issue is particularly relevant to the evaluation of herbal therapies where practitioners may be even more reluctant to randomization of their patients.

Analysis Issues

Identification of objective outcomes, difficulties of blinding interventions, investigators and patients are a major challenge particularly in those herbal therapies used within an alternative medicine system such as Ayurveda or traditional Chinese Medicine. Both systems for example rely on the training, ability and knowledge of the practitioner and analyzing individual approaches may be cumbersome. Experienced practitioners will know which treatment is hypothesized to be active.

Duration of trials should also be carefully considered since it is known that most herbal products require an "initiation period to start working" that might be highly variable and this may affect final analysis of the trial.

Individual differences in highly individualized therapies and patient-provider relationship may influence outcomes. One way to overcome this challenge may be by imposing constraints on the patient-treatment provider interaction; monitoring these interactions by a third party; and evaluating the practitioner-patient relationship across treatment groups [Horvarth, 1989]. In evaluating response, data for all patients entered into the clinical trial should be included.

REFERENCE - ***GMP for Botanicals***