

**EVALUATION OF GUIDELINES FOR CLINICAL TRIALS OF
TRADITIONAL PLANT MEDICINES.**

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Worldwide interest in natural medicine is on the increase and the use of natural/traditional products is growing at a staggering rate. The WHO estimates that 4 billion people (80% of the world population) use herbal medicine for some aspect of primary health care. These herbal products are however mostly used without the necessary clinical trials done to prove their pharmacological activities and, therefore, their quality, efficacy and safety. Furthermore, of the 50 000 clinical trials currently conducted in the USA, only a small percentage are being done on herbal medicine.

It was the objectives of this study 1) to review the current international guidelines for the evaluation of herbal medicine; 2) to gain a perspective on the number, type and quality of clinical trials that have been done on herbal medicine and to adopt a set of guidelines that could be used to conduct a trial on a traditional herbal medicine used in South Africa. To verify these guidelines, 3) a protocol for a clinical trial was drafted and submitted for approval to the regulatory and ethical authorities in South Africa. The final objective of this study was 4) to determine the acceptability by clinical investigators and trial subjects of the afore-mentioned drafted clinical trial.

To realize these objectives literature searches were done on the guidelines for herbal medicine clinical trials as proposed by the health departments of the World Health Organization (WHO); Food and Drug Administration; European Union; New Zealand; Canada and South Africa. Literature searches were also done on the number, type and quality of clinical trials done on herbal medicines. To assess how South Africa deals with clinical trials on traditional plant medicines a protocol to test the anti-asthmatic efficacy of a traditional herbal plant was developed and submitted for

approval to local ethics committees and the Medicines Control Council of South Africa. Medical professionals and trial subjects were also asked for their opinion on the acceptability of clinical trials on herbal medicines.

The results showed that the guidelines for clinical trials on herbal medicines (if any existed) varied from the one regulatory agency to the other, but they did not differ fundamentally from the guidelines used for pharmaceutical trials. The absence of toxicological studies was the major controversial issue regarding plant medicine trials. The WHO and FDA were the only agencies that advocated historical use of the product as adequate safety data. It is their opinion that *prolonged and apparently uneventful use of a substance usually offers testimony of its safety*.

Further, the review of the clinical trials that have so far been done on herbal medicines confirmed the current status that these trials are generally of poor quality, that the quality of the tested products were not standardized and thus highlighted the need for more research in this area.

Based on the information gained from the reviews of the international guidelines for, and the already completed clinical trails on herbal medicine (including 17 specific for asthma), it was possible to develop a full protocol for a pilot study on mild to moderate asthmatic subjects to test the bronchodilatory effect of the herbal medicine, *Artemisia afra*. It was to be a 24- week randomized, single blind placebo-controlled crossover design study. In South Africa however, the ethics committees and MCC could not approve the submitted protocol for the mentioned study, mainly due to the fact that no safety data on the plant medicine was available.

Finally, it seemed that the medical professionals involved in clinical trials as well as the public were ready for clinical trials on herbal medicines.

The overall conclusion drawn from this study was that South Africa lacked the necessary guidelines for clinical trials on natural/herbal medicines. If the WHO guidelines can be adopted in South Africa to approve clinical studies without the need for stringent safety data, clinical trials on herbal medicine can be done in parallel with pharmaceutical products. Evidence of the efficacy of traditional herbal medicines may then be factual and not mere opinions.



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KEYWORDS

Guidelines for Clinical Trials

Traditional Herbal Medicines

World Health Organisation

International Conference of Harmonisation

Good Clinical Practice

Protocol

Artemisia afra

Medicines Control Council

Ethics Committees



DECLARATION

I declare that *The evaluation of guidelines for clinical trials of traditional plant medicines* is my own work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged as complete references.

Anthea van Wyk



Signed:

September 2005

ACKNOWLEDGEMENTS

I dedicate this book to my husband, Francois and sons, Jean and Braam who allowed me to be myself – the eternal learner.

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To God be all the glory!



A study that goes unpublished has no more value than one never done.

DEFINITIONS WITH REGARDS TO HERBAL MEDICINES AND CLINICAL TRIALS

In order to meet the demand for the establishment of standard, internationally accepted definitions are given:

Herbal drugs are mainly whole, fragmented or cut plants or part of plants in an unprocessed state, usually in dried form, but sometimes fresh. Herbal drugs are precisely defined by the botanical scientific name according to the binomial system – genus, species, and variety.

African traditional medicine may be described as the total body of knowledge, techniques for the preparation and use of substances, measures and practices in use, whether explicable or not, that are based on the socio-cultural and religious bedrock of African communities, are founded on personal experience and observations handed down from generation to generation, either verbally or in writing and are used for the diagnosis, prevention or elimination of imbalances in physical, mental or social well-being.

Traditional healers are persons recognized by the community in which they live as competent to practice medicine. There is a social consensus conferring a special status (given different names depending on language concerned) on such healers and according them the power to heal or even to prevent illness or any other misfortune or to promote the happiness of those consulting them.

Complementary and Alternative Medicine, as defined by the National Centre for Complementary and Alternative Medicine (NCAM), is a group of diverse medical and health care systems, practices and products that are not presently considered to be part of conventional medicine.

Traditional use of herbal medicine refers to the long historical use of these medicines.

A *Clinical trial* is a research study in which a treatment or therapy is tested in people to see whether it is safe and effective. Each trial follows a protocol – a written, detailed plan that explains why there is a need for the study, what it is intended to do and how it will be conducted. Randomised trials gives the best chance of knowing that the study results are caused by the treatment and not some other factor, such as people's choices or beliefs. Each participant in a randomised trial is assigned by chance (through a table of random numbers) to one of two groups:

- The investigational group, made up of people who will receive the therapy, also called the active treatment; or
- The control group, made up of people who will receive either the standard treatment (if there is one) for their disease or a placebo.

Trials can be double blind. This means that neither the researcher nor the participants know who has been assigned to which group. Blinding is another way to help minimize the chance of bias influencing the trial results.

A *Placebo* is designed to resemble as much as possible the treatment being studied in a clinical trial, except that the placebo is inactive.

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ABBREVIATIONS

ARGCM	Australian Regulatory Guidelines for Complementary Medicines
BP	British Pharmacopoeia
CAM	Complementary and Alternative Medicine
CIOMS	Council for International Organizations of Medical Sciences
DoH	Declaration of Helsinki
EU	European Union
FDA	Food and Drug Administration
FDR	Food and Drug Regulations
GCP	Good Clinical Practice
GCRP	Good Clinical Research Practice
HMPC	Herbal Medicinal Products Committee
HREC	Human Research Ethics Committee
ICH	International Conference of Harmonization
IRB	Institutional Review Board
MCC	Medicine Control Council
NCCAM	National Center For Complementary and Alternative Medicine
NIH	National Institutes of Health
TGA	Therapeutic Goods Administration
US	University of Stellenbosch
UWC	University of the Western Cape
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

There is a worldwide tendency to return to the use of alternative medicine in primary health care. In South Africa alone, about seventy percent of the population uses some form of natural or traditional herbal medicines.¹ The problem is however, that the market is flooded with allopathic products, but clinical trials to prove the safety and efficacy of such herbal medicines are rarely done and when done, frequently seriously flawed.

The Declaration of Helsinki (developed by the World Medical Association) and the drug regulatory authorities of countries (e.g. the Medicines Control Council of South Africa, the Food and Drug Association in the United States, etc) have formulated guidelines and regulations which provide guidance to physicians and other participants conducting medical research involving human subjects. It is generally argued that the ethical, legal and regulatory requirements for research and clinical trials with herbal medicines on human beings should not differ in standard from that set for regular pharmaceutical clinical trials. It is unclear however, to what extent there exist harmonization between the guidelines of different authorities and if the guidelines differ from that of conventional pharmaceutical trials.

There is also very little information on completed clinical trails on plant medicines, apart from the general impression that the overall quality of evidence for alternative medicine randomized clinical trials is poor and even those trials done on traditional Chinese

medicine needed urgent improvement.⁴ For clinical evidence of safety and efficacy the placebo-controlled, double blind randomized trial may be considered the gold standard, even for herbal medicine. However, randomized clinical trials on herbal medicine may be particularly difficult to do in that it needs large volunteer groups, is of long duration and requires expensive healthcare services. Moreover, the problem exists that funds for such trials, is usually not readily available. In South Africa where a large number of the population uses traditional plant medicines a clear perspective on the current status of the clinical trials of plant medicines is thus needed.

Given the above, the first two objectives of this study were thus to establish whether there are differences in the international guidelines for trials with pharmaceutical and traditional herbal medicines and to gain a perspective on the number, type and quality of clinical trials that have been done on herbal medicine in general and anti-asthma herbal medicines in particular. A third objective was then, from the information gathered to formulate or adopt guidelines that could be used to conduct a clinical trial on a locally used plant - *Artemisia afra*. Finally, to verify the feasibility of these guidelines a protocol to conduct a clinical trial to test the efficacy of this herbal plant, was to be drafted and submitted to the regulatory authorities of South Africa.

The reason for the focus on the treatment of asthma is because asthma is one of the most common chronic diseases in modern society and there is increasing evidence to suggest that its incidence and severity are increasing. There is a high prevalence of usage of complementary medicines, such as herbal preparations for asthma. Physical evidence of

the use of herbal remedies of asthma dates back approximately 5000 years. Four out of five classes of drugs currently used to treat asthma (β_2 -agonists, anticholinergics, methylxanthines and cromones) have origins in herbal treatments.² Historically, *Artemisia afra* has been used to treat respiratory illnesses, including asthma, coughs, bronchitis and influenza.³ It is however a fact that as far as plant medicines are concerned opinion dominates over evidence.

Finally, due to the popularity of herbal medicine, it is in the interest of the public for research in this field to be supported by investigating the guidelines and procedures necessary for clinical trials. Without the knowledge obtained from clinical trials, people using herbal medicine may be at risk for serious effects from taking the wrong dose, using the treatment in the wrong way or using it with other treatment with which it may interact. Furthermore, the results of randomized clinical trials on herbal medicine might go a long way to uncover new knowledge that will lead to better health for everyone.

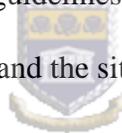
CHAPTER 2

BACKGROUND

First the word, then the plant, lastly the knife.

Aesculapius of Thassaly, Greek God of Healing, circa 1200BC.

In the light of this study into clinical trials on herbal medicines it was important to look at the history and modern day use of alternative and herbal medicine. This chapter will therefore cover the following issues regarding alternative medicine: historical overview; current level of use; problems associated with herbal product use; status of clinical trials done on alternative medicines; current guidelines on clinical trials of alternative medicine and the regulatory authorities involved and the situation in South Africa regarding traditional herbal medicine.



2.1. THE HISTORICAL PERSPECTIVE

Mankind has been using plants as medicine since the beginning of time and plants have long been viewed as a healing “gift” from God. In the 1500’s, Paracelsus, an alchemist, became the founder of modern pharmaceutical medicine. In the early 1600’s an English pharmacist published a book that recommended that patients grow their own herbs rather than buy expensive exotic or imported drugs. The book was published in the time when professional physicians viewed herbal medicine as contemptuous. In the mid 1800’s, the medical system we now refer to as “biomedicine” began to dominate orthodox medicine.⁵

Growth of the modern pharmaceutical industry was assured by the downfall of natural forms of healing and the emphasis on biomedicine.

As recently as 1960, a burial site of a Neanderthal man revealed eight different species of plant material that had been gathered by the community to treat man. Seven of those species are still used for medicinal purposes today. More than one quarter of prescription medicines have been developed from herbs, i.e. aspirin from white willow bark (*Salix alba*), the first narcotic from the opium poppy and the birth control pill from the Mexican plant *Dioscorea villosa*.

Currently, modern society is, for various reasons – such as costs, dissatisfaction with medical outcomes, changing values about health  (a more holistic approach) and increased access to health information with the help of modern technology – such as the Internet, returning to the use of traditional plant medicine.

Dissatisfaction with the medical outcome primarily appears to stem from those instances where orthodox medicine has been unable to provide effective treatment of or relief from symptoms or has caused adverse side effects. People who experience dissatisfaction or limited success with the outcome of orthodox medicine and turn to complementary medicine most commonly have conditions associated with chronic pain (back and neck injuries, arthritis and rheumatism) or illnesses such as cancer.⁶

The use of complementary medicine has also been linked to people's dissatisfaction with the doctor-patient relationship. These people may feel that medical practitioners no longer allow enough time to discuss health concerns, do not listen to their patients and do not provide adequate explanations and information concerning health problems and the treatment options available. This is in contrast to complementary medicine practitioners, who generally have longer consultation times and focus on gaining information from the patient regarding their lifestyle as well as actual symptoms.

A number of theorists have also proposed that our increased use of complementary medicine is related to an overall change in our values and beliefs about health, more specifically a shift to a more holistic view of health encompassing the mind, body and spirit. Whereas orthodox medicine deals primarily with treating the symptoms, complementary medicine looks at the person as a whole (lifestyle as well as physical and emotional health). The need for individuals to become responsible for their own health care is now also more widely recognized. This is closely tied to an increased interest in health prevention strategies such as diet, exercise and stress management, all which involve people changing their lifestyle and behaviors.

Improved access to the Internet has also contributed to an increase in complementary medicine use. The Internet provides people with the opportunity to gather a range of information on various health topics. This increased access to health information has a number of consequences. Firstly, it can assist people to gain a better understanding of their health issues and enable them to discuss their health concerns and preferences with

their doctor. Having an adequate knowledge of the issues involved allows people to participate more fully in consultations with their doctor and provides them with the confidence to discuss the option of complementary medicine. Secondly, the Internet is an important marketing tool for complementary medicine. A large number of web sites are dedicated to the promotion of various complementary medicine products, in particular herbal medicine preparations. Many of these sites include anecdotal evidence from people who have used the products and found them to be “therapeutic”.

The popularity of complementary medicine has also been enhanced by the growth of research into their safety and effectiveness, although a lack of scientifically valid research into complementary medicine has always been a significant barrier to orthodox medicine accepting these health care approaches.  Recently, however, there has been an increase in research into complementary medicine. This increase in research has in turn lead to more orthodox medical professionals accepting complementary medicine. Many general practitioners now refer their patients to complementary health practitioners. Similarly, some general practitioners are undergoing training in the area of complementary medicine, recognizing that it provides a useful addition to their practice.⁷

Much of the growing interest in herbal medicine stems from the increased knowledge obtained from the active components (phytochemicals) of herbal plants. Since the 1950's analytical techniques have been developed to allow the identification of these active components in individual plants. Evidence is surfacing that herbal plants can play a positive role in health maintenance and disease prevention. Protective anti-oxidants are

now recognized to include phytochemicals such as flavanoids, carotenoids, coumarins, etc. and fruit and vegetables are good sources of these substances and herbal plants are presumably even richer in these sources. Since the 1980's scientists have become increasingly confident that fruit, vegetables and herbal plants have protective effects against life threatening disease like cancer.⁸

It seems that the way plant medicine has been viewed from the beginning of life until modern human times has now gone full circle.

2.2 THE CURRENT LEVEL OF USE

The World Health Organization (WHO) estimates that 4 billion people – 80% of the world population - use alternative medicine for some aspect of primary health care. Researchers concluded that by 2010 at least two-thirds of the United States population would be using one or more of the approaches we now consider alternative or complimentary.⁹ In South Africa more than 70% of the population uses alternative or traditional medicine.¹ These are obtained from a traditional healer, purchased from herb sellers or gathered in the wild for self- medication.

A recent survey identified herbal use as the fastest growing category of complementary medicine in the United States. In 1997 it was estimated that the total sales of herbs in outlet stores (i.e. grocery stores, pharmacies, mass merchandising retail stores) had increased by a dramatic 79.5% since 1996. A telephonic survey of 2055 adults in the

USA showed that the total annual out-of-pocket expenditure on all alternative therapies was in the region of \$27 billion. This sum is in addition to costs reimbursed by medical aid funds. In the UK the annual expenditure on complementary and alternative medicine for the whole UK population was estimated to be in the region of £1.6 billion per annum even though conventional medicine is available free to all. This represents about 4% of the UK public expenditure on health.¹⁰

By 1993, an estimated \$621 million was spent by Australians annually on complementary medicines and a further \$309 million on complementary health practitioners. In the same year approximately \$360 million was spent on pharmaceutical drugs. A comprehensive study that was done in that year in Australia, revealed that almost half of the respondents (48.5%) had used at least one non-medically prescribed complementary medicine in the past year (excluding calcium, iron and prescribed vitamins) and that 20.3% of the respondents had visited at least one complementary health practitioner in the same period. In each of these countries, this money was spent by members of the public in addition to their personal contribution to health insurance schemes. Health insurance providers in some countries (e.g. UK and USA) are also increasingly willing to include some alternative medicines in their provision.¹¹

The conclusion can thus be made that with the increase interest in alternative medicine and the subsequent increase in use, large amounts of money is spent on complementary medicines.

2.3 CURRENT PROBLEMS ASSOCIATED WITH HERBAL PRODUCT USE

A common problem associated with the use of herbal medicine is that many people think that anything natural is safe and then fail to take the same precautions they would with pharmaceutical medicine. This attitude can cause people to ignore adverse reactions. For instance, they may not follow the directions for use and take higher dosages, something they would not do with prescription medication or people may tend to treat themselves instead of consulting a health practitioner. In one study conducted in Australia, fewer than 50% of people told their medical practitioner they were using a complementary medicine.¹² It is also true that people using herbal medicine may delay the use of necessary pharmaceutical treatment for health problems such as cancer – where the advantages of early detection may be lost.



Another problem with the use of herbal medicines is the fact that it is not always clear whether interactions exist between herbal medicine and other medicinal products or substances like alcohol, caffeine, tobacco or nicotine. Herb-drug interactions may be pharmacodynamic or pharmacokinetic. Pharmacodynamic interactions could occur when a herbal product and a pharmaceutical drug have similar or antagonistic pharmacological effects or adverse effects. When the herb alters the absorption, distribution, metabolism or excretion of the pharmaceutical drug, pharmacokinetic interactions may occur.¹³

The Uppsala Monitoring Centre of the WHO looked at 2487 cases of suspected adverse reactions to herbal medicines reported over a period of 20 years.¹⁴ Twenty one (0.8%) of

these cases had a fatal outcome. There is a definite lack of public awareness to report adverse reactions when using herbal medicines and patients are reluctant to provide information regarding their use of herbal products to their healthcare professionals.

The problem also exists that in the absence of adequate regulations, it is possible that some providers of herbal medicine will not adhere to adequate standards of clinical practice. This can have obvious safety implications. The issues associated with safety and quality of herbal medicines include toxic herbs, contamination with heavy metals, microbial organisms, and other contaminants (such as pesticides) as well as deliberate combination (adulteration) with pharmaceutical products.

A further problem with research on alternative medicine is the fact that complementary health practitioners question the suitability of randomized clinical trials in relation to complementary medicine because of the holistic approach (i.e. treating mind, body and spirit at the same time) that is required and the fact that the alternative medicine is normally tailored specifically for each individual. Practitioners suggest it is inappropriate to only test one treatment in isolation and to give it to all participants in the same manner and amount, as occurs in randomized clinical trials. Also, finding an appropriate placebo – another typical feature of randomized clinical trials – for certain complementary therapies is difficult. In a placebo-controlled clinical trial half the subjects (the control group) receive a ‘dummy’. It is scientifically recognized that the average proportion of people that respond to a placebo is 33%, although this figure can be higher or lower depending on the type of treatment being tested even under the best of circumstances.¹⁵

Consequently it is difficult to determine if any positive effects attained are a result of the product being tested or just a placebo effect and complementary medicine practitioners would argue that the mind is also important in the healing process.

2.4 STATUS OF RESEARCH ON ALTERNATIVE MEDICINE CLINICAL TRIALS

Due to the fact that plants cannot be patented, very little research has been performed on plants as medicinal agents. In the USA the process of demonstrating drug safety and efficacy of a new pharmaceutical takes approximately 15 years and costs an estimated \$500 million and only few research companies are willing to fully invest the time and money necessary to satisfy the FDA requirements.¹⁶



It is therefore clear that the regulatory requirements for proof of safety and efficacy generally make it uneconomical for the private industry to conduct costly clinical trials on herbal medicine. If, however, the regulatory requirements regarding efficacy can be relaxed, private companies might more easily pursue research into issues of safety and quality control of herbal medicine. Public funding might still however be needed to confirm the validity of herbal remedies, because pharmaceutical companies would have little incentive to develop a herbal product that might displace a patented drug.

Apart from those herbal plants that have high levels of toxic alkaloids, the data for the vast majority of herbal medicine indicate that they have low toxicity. It is therefore

argued that more data is needed to assess the *efficacy* than to assess *safety* of herbal medicine and, for proof of efficacy, the clinical trial has become the gold standard to us. In fact it is argued unless a study has been conducted on human subjects, no pertinent conclusion on its efficacy and or safety can be drawn.

The use of randomized clinical trials for herbal medicines are often difficult since it needs large volunteer groups, are of long duration, require expensive healthcare professionals and as mentioned before, funds for such trials are usually not readily available. Further, the infrastructure for alternative and herbal medicine research is largely non-existent.

The general lack of cooperation between the traditional healer and the professional medical doctor also does not help research in this field. There is a considerable suspicion between the health professions and the healers. At present there is one traditional healer to every 500 inhabitants in comparison to one doctor for every 40 000 inhabitants in South Africa which indicates a social consensus conferring a special status on such healers and according them the power to heal or prevent illness.¹⁷ It is therefore apparent that if research in this area is to be conducted effectively, it must be directed to a public health goal.

2.5 CURRENT GUIDELINES AND REGULATORY AUTHORITY

DIRECTIVES FOR CLINICAL RESEARCH ON ALTERNATIVE MEDICINE

Herbal products are mainly marketed as supplements and currently no rigorous regulations, comparable to that required in the pharmaceutical sector, apply. This seems to be mainly so because, firstly, the practice of traditional medicine that is influenced by factors such as culture, history, personal attitudes and philosophy, vary greatly from country to country. Secondly, documented evidence of traditional use of herbal medicine, including modern use, is for regulatory purposes not given enough credit as evidence for continued human use.

The World Health Organization is the umbrella organization of the world under which most countries operate and take their guidance from as far as health issues are concerned.  As recently as 1997, the World Health Organization drafted the *Guidelines for methodology on research and evaluation of traditional medicine*. Since then the draft had been revised four times and the most recent recommendations were developed in April 2000. These guidelines were formulated from the comments on questionnaires received from experts world wide. The guidelines were however, intended to be modified by each WHO member country to meet their specific needs and for the guidelines to serve as a reference source for researchers and health authorities. Presently the WHO is also in the process of compiling a World Pharmacopoeia of widely used traditional herbal medicines that is expected to further assist research in the field of herbal medicine.

2.6 SITUATION IN RESPECT OF TESTING A PLANT MEDICINE IN SOUTH AFRICA.

As far as plant medicine is concerned, South Africa is considered to be a "hotspot" for biodiversity and more than 22 000 plant species occur within its boundaries. This represents 10% of the world's species, although the land surface of South Africa is less than 1% of the earth. Approximately 3 000 species of plants are used by an estimated 200 000 indigenous traditional healers.¹⁸ Due to urbanization, a large informal trade business with medicinal plants has been established. Unfortunately, utilization of the plants has depleted the wild populations, resulting in many plant species being considered vulnerable, and being lost from their natural habitat. One of the present concerns is to protect and preserve native South African plants and the traditional healing system of South Africa by identifying and cultivating regional medical plants. It is a fact that displaced rural people who are immigrating to urban areas such as Cape Town and Johannesburg no longer have access to the traditional medicines - which have formed much of the basis of their self-care. At the same time, the increasing demand for wild South African medicinal plants for export and domestic use has created great environmental pressure on local plant populations. This situation has forced the closing of some areas to collection, further increasing the pressure on other areas. Exhaustion of botanical resources presents a threat not only to the environmental well-being and biodiversity of South Africa, but would result in the elimination of the traditional medicinal system on which such a large proportion of the population depends.

At present no official legislation exists, but a proposed law known as the "*Protection of Indigenous Knowledge Act*" is being prepared to advance the promotion and protection of indigenous knowledge. Communities fear the illicit use and exploitation of indigenous knowledge by outsiders, with the result that most knowledge and especially indigenous medicinal plant knowledge is being kept secret. The proposed act will lay ghost to this fear, as the law should now protect the individuals and communities.

South Africa has never had its own pharmacopoeia and the pharmaceutical professions use the British Pharmacopoeia (BP) and that of Europe and the United States. Only two South African medicines have ever been included in the BP Monographs.¹⁹

As far as the testing of herbal plant medicine is concerned, the Medical Control Council (MCC) is the governmental regulatory authority in South Africa and no clinical trial can be conducted without the approval from the ethics committee. Although the Guidelines for Good Clinical Practice (GCP) for pharmaceutical trials exist, clinical trials on complementary/traditional herbal medicine have not yet been specifically addressed, as it was never before done officially in South Africa. It is therefore an open field that is in need of attention and groundbreaking work still needs to be done.

CHAPTER 3

PLAN OF WORK

In the light of a worldwide consensus that alternative medicine should be regulated in some way, the first objective of this study was to review the current international guidelines for the evaluation of traditional herbal medicines. As a second objective, it was also necessary to gain a perspective on the number, type and quality of clinical trials that have been done on herbal medicines and to adopt a set of guidelines that could be used to conduct a clinical trial on a locally used plant. Thirdly, to test the usefulness of the adopted guidelines a protocol for a clinical trial on a traditional herbal medicine was to be prepared and submitted to the regulatory authority and ethical committees in South Africa. Clinical investigators and clinical trial subjects were also to be interviewed to obtain their opinion on the acceptability of a clinical trial on herbal medicine.

To realize the first objectives the guidelines pertaining to clinical trials on herbal medicines issued by the FDA, MCC, European, Canadian, Australian, New Zealand and the WHO regulatory authorities were to be examined and compared for similarities. The afore-mentioned are the most influential agencies in the medical field in the world and from this review the most appropriate guidelines could therefore be adopted. To realize the second objective the medical literature was to be searched for all trials on herbal medicines and specifically those used for the treatment of asthma. The clinical trials done

on herbal medicine for asthma were to be reviewed to gain insight into the overall efficacy (if any) of the products and to determine the quality of these trials in comparison to that of clinical trials done on regular pharmaceutical medicine. To realize the third objective of this investigation, a protocol was to be developed for a clinical study to evaluate the efficacy and safety of a herbal preparation – *Artemisia afra*. This plant is widely used for asthma and the clinical evaluation thereof could prove to be valuable. To determine whether the adoption of internationally recognized guidelines could be used to develop a protocol that would be acceptable in South Africa, the protocol based on the internationally recognized guidelines, were to be submitted to the Medical Control Council and ethics committees in South Africa for their for approval. Finally, the acceptability of the protocol for a clinical trial on the herbal medicine to both clinical investigators and clinical trial subjects was to be investigated through informal and non-validated interviews that also sought to determine their willingness to take part in such a clinical trial on an alternative medicine.

It was believed that the results of this study would go a long way towards determining the viability of clinical trials on herbal medicines and establishing what is needed in terms of regulations, the expertise, experience and facilities for the systematic clinical verification of the many claims made for herbal plant medicine in South Africa.

CHAPTER 4

METHODS

In this chapter the methods used to (1) obtain information on the international guidelines for clinical trials, clinical trials done on herbal medicine and the design and development of a clinical trial on a herbal medicine as well as (2) the actual preparation and submission of the clinical trial protocol for ethical and regulatory approval are discussed. The acceptability of a clinical trial on herbal medicine by clinicians and participants was also investigated.

4.1 Search for Information on Clinical Trial Guidelines

Essentially two types of searches were performed: one via the Internet and one of the sources obtainable via an academic library.

First, a search for literature and information on the guidelines in general for clinical trials internationally provided by the regulatory authorities of various countries was performed via the Internet. The main search engines used were Medline, Pubmed, and Google. Searches were conducted during February and August of 2003 to collect the information necessary to prepare the protocol that had to be ready for submission before September 2003. In addition the specific guidelines for clinical trials on herbal medicines provided via the Internet by the following regulatory authorities were also traced, read and analyzed: the Food and Drug Administration (FDA) of the United States, the World Health Organization (WHO), the New Zealand, Canadian and Australian regulatory authorities, the

Council of the European Union and the Medicines Control Council (MCC) of South Africa. For this search the following search terms were used: *guidelines clinical trials herbal medicine* and in total the following websites were searched for information: www.pubmed.com; www.medline.com; www.google.com; www.fda.gov; www.who.int; www.emea.eu.int; www.medsafe.govt.nz; www.ich.org and www.mccza.com. The information obtained in these searches was in the form of abstracts, articles and official documents which was then stored as computer files for future reference and also printed for easy access.

Secondly, the library of the medical school of Stellenbosch (Tygerberg Campus) was visited and literature on clinical trials involving traditional herbal medicines and the guidelines for clinical trials on herbal medicine located, read and analyzed. Books, theses, journals, articles and periodicals on the topic of traditional herbal medicine and found within the traditional medicine section of the library were searched.

The information collected from each search was read with the focus on the latest guidelines for clinical trials and with specific reference to clinical trials done on herbal medicine. The guidelines from each regulatory agency was then summarized and tabulated under headings such as safety data required, product validation, dosage form, informed consent, ethics issues, etc., and investigated for differences in these criteria between the sources. Finally, a summary of the guidelines that were common to all the sources and that could be followed for the design of the trial on the herbal medicine (*Artemisia afra*) was drawn up.

4.2 Search for information on clinical trials conducted on herbal medicine

Similar Internet and library source searches were done to retrieve information on clinical trials done on herbal medicine (in general) and trials done on herbal medicine for asthma. Again, these searches were done in the first semester of 2003 and the search terms used included: *clinical trials alternative medicine*; *clinical trials traditional herbal medicine*; *clinical trials asthma* and *clinical trials herbal medicine asthma*.

The websites visited for these searches included: www.clinicaltrials.gov; www.google.com www.medline.com; www.pubmed.com; www.ncbi.nlm.nih.gov; www.altmed.od.nih.gov; www.bmj.com; www.ije.oupjournals.org; www.doh.wa.gov and <http://thorax.bmjournals.com>.

The collected information was read, analysed for the number and type of studies that could be located, for adherence to the conventional criteria for pharmaceutical trials, the types of outcomes attained, flaws in the protocols and any recommendations that were made regarding the clinical evaluation of herbal medicines.

4.3 Design of a protocol for a clinical trial on *Artemisia afra*.

Using the information obtained on the guidelines for trials on herbal medicines (section 4.1) and reported trials already conducted on herbal medicines (section 4.2) a protocol for an efficacy study on *Artemisia afra* was written. In this protocol specific attention was given to the following aspects of the protocol: the

study design; the study objective; endpoints; subjects; inclusion and exclusion criteria; the trial material; statistical analysis; patient information and consent forms. The protocol had to be executable, meet the criteria for acceptance by the ethics committees and regulatory authority, be useful to recruit volunteers, and be acceptable to trial investigators.

The protocol was to be for a pilot study to test the anti-asthmatic effect of the herbal plant *Artemisia afra* in mild to moderate asthmatic subjects. For the purpose of this investigation it was decided to do a 24-week, randomized, single blind, cross over study and the endpoints included efficacy and safety. It was also necessary to consider exclusion and inclusion criteria on grounds of gender, age, disease risk factors and medical history, stage of disease and concomitant medication. To make sure that this study was of a high standard, it was preferable for the study to be randomized, placebo controlled and double-blinded. The quality and dosage form of the *Artemisia afra*, herbal preparation was also a very important aspect of the study design.

To show that a reasoned argument had been made in estimating the volunteer/subject numbers for the clinical trial, data from a similar study (on a pharmaceutical product) was used to predict variability (e.g. standard deviation) of the primary outcome. A statistician and other reference trials were consulted to argue at what would be a meaningful change in the primary endpoint to be produced by the herbal plant compared to that by the placebo. The number of

volunteers was calculated to give a specified significance level with a known power (e.g. significance at the 5% level with 90% power).

Finally, a Patient Information leaflet and consent form was designed to accompany the protocol and to adequately inform the volunteers/subjects of the aims, methods, sources of funding, potential hazards/discomforts the study may entail and their freedom to withdraw consent. An information brochure/investigators brochure on the plant *Artemisia afra* was not available since no safety and other data has yet been collected and could therefore not be included in the design for the protocol. The protocol and its accompanying documents (Patient Information leaflet etc) was prepared as printed copy and electronic version.



4.4 Testing of the acceptability of the *Artemisia afra* study protocol

The acceptability of the designed protocol was tested by submitting it for ethical and regulatory approval as well as acceptance by trial subjects and trial investigators.

4.4.1 Submission of clinical trial of *Artemisia afra* for regulatory approval

First, the Medicines Control Council specifications for the application and its submission were obtained from the regulatory authority via the Internet at www.mccza.com. Then all the necessary completed forms as well as copies of the protocol, patient information leaflet, a covering letter, the *Curriculum Vitae* of

the investigators and monitor, insurance details and recruitment advertisements were prepared (section 4.3) and couriered to The Registrar in Pretoria strictly following the MCC submission rules. Since no safety data on the study plant existed, literature indicating evidence of use and the dosage forms of the herbal plant were included in the submission. The deadline for submission of the application was 28 September 2003 for review by the MCC in November 2003. The documents were then duly posted by courier service and confirmation of the delivery by the courier company and receipt of the application by the MCC sought thru telephonic enquiry and dates and outcomes of these events, recorded. Complete copies of the submitted application was also filed and kept as a reference. It was anticipated that a response would be obtained from the MCC within a week or two after the meeting scheduled on 5 November 2003. The decision from the MCC was expected to be in the form of a written approval or recommendations, but what actually transpired are discussed in Chapter 5.

4.4.2 Submission of *Artemisia afra* clinical trial protocol for ethical approval.

Submissions for approval of the protocol were also made to two ethic committees – The Pharmaceutical Trial Committee, University of Stellenbosch, Faculty of Health Science IRB and Pharma-Ethics an Independent Research Ethics Committee, Pty Ltd Bloemfontein - in February and March 2004, respectively. The specifications for the applications to the ethical committees of Tygerberg (Cape Town) and PharmaEthics (Bloemfontein), were obtained via electronic mail

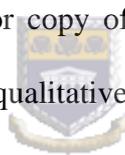
from the following website and address, www.sun.ac.za and barbara@shibboleth.co.za, respectively.

The application to the Committee for Pharmaceutical Trials at The University of Stellenbosch (Tygerberg Campus) was hand delivered on 12 February 2004 to the Manager of Pharmaceutical Trials. Again the completed application, the checklist, covering letter and required CPT04 Form were handed in with copies of the Protocol, Patient Information Leaflet, CV's of investigators and monitor, insurance details and recruitment advertisements. The application to PharmaEthics, the second ethics committee was submitted to obtain another view on the ethical acceptability of the proposed clinical trial. Again, the requirements for submission was followed and the following documents couriered: the completed application form, covering letter, copies of the Protocol, Patient Information Leaflet, CV's of investigators and monitor, insurance detail and recruitment material. In this case a diskette with the Protocol, Investigators brochure, Patient Information Leaflet and the application fee of R5500.00 had to accompany the application. The receipt of the application was confirmed telephonically. This committee had meetings every two weeks and a response, in written form, was therefore expected during March 2004.

Complete copies of the applications to both Independent Regulatory Bodies were filed for future reference and to monitor the application process. The complete process from the design of the protocol until the final submissions at the ethical and regulatory committees took seven months.

4.4.3 Testing of subject acceptance of a clinical trial on herbal products.

For ethical and regulatory reasons patients could not be asked for their views on an ethically unapproved protocol. However, for this part of the study approximately twenty randomly selected mild to moderate asthmatic patients familiar with clinical trials were interviewed at a clinical trial centre to determine their views regarding participating in clinical trials on herbal medicine in general. The design of the trial was only discussed in general, with no trial specific details being given as the clinical study was not yet approved by the regulatory authority. Their views were solicited using a questionnaire covering questions regarding their participation in previous pharmaceutical clinical trials, participation in trials on herbal medicine, their usage of herbal products and views regarding trials on herbal products. See Table 6 for copy of the questionnaire. Their responses to each question was recorded and qualitatively assessed for general trends.



4.4.4 Clinical investigator acceptance of a clinical trial on herbal medicine

Two clinical investigators were approached to give their opinion on the feasibility of a clinical trial on a herbal plant that has traditionally been used for the relief of asthma symptoms. They were a Professor of Pulmonology – a pioneer in the field of clinical trials on patients with pulmonary diseases - and a general practitioner who has been involved in clinical trials on conventional pharmaceutical medicine for more than four years. After having had time to view protocol documentation, the professor was, in a verbal interview, asked to give his opinion on the merit of the protocol and study design and the necessity of studies on herbal medicine. His

willingness to be clinically involved in trials on herbal products was also discussed.

The General Practitioner was similarly asked to give an opinion on the feasibility of the clinical trial, the availability of volunteers/patients to participate in the trial, funding and time needed to do such a trial as well as her willingness to be involved in clinical trials on herbal medicines. In both cases the comments of the clinical investigators were summarized.



CHAPTER 5

RESULTS AND DISCUSSION

In this chapter the results of the website searches of the literature reviews of the international guidelines on clinical trials for herbal medicine and clinical trials done on herbal medicine as well as the writing and submission of the protocol for a trial on herbal medicine are given and discussed.

5.1 CURRENT ASPECTS OF REGULATORY GUIDELINES

Finding the information regarding guidelines on clinical trials for herbal products on the websites visited was not always without difficulty. To access the websites for the regulatory authority was in itself not problematic, but to find the department that dealt with the specific subject was a time consuming process. Furthermore, the regulatory bodies of some countries, like China, could not be consulted, as most of the addresses found on the Internet were only accessible for Chinese literate visitors.

The analysis of the guidelines for clinical trials on herbal medicine used in Europe, Australia, the United States, Canada and South Africa indicated that the following approaches are currently being practiced by the relevant regulatory agencies. The practices were analyzed and compared in respect to the following areas – product validation, informed consent, safety data, product dosage form and ethical issues. The findings for each agency are discussed below and summarized in Table 2.

5.1.1 Food and Drug Administration (FDA) – USA

The FDA is the main authority agency within the Department of Health in the USA and consists of eight centers – including the Center for Drug Evaluation and Research (CDER) and the National Institutes of Health (NIH). The National Center for Complementary and Alternative Medicine (NCCAM) is one of the 27 centers that in turn make up the National Institutes of Health (NIH). When visiting the www.fda.gov site, a description of the different centers and agencies within the organization and the FDA activities are given. The CDER home page included guidelines, but no specific mention was made of botanical or herbal products. It did however have a search function and when this is used the words *botanical drug products* lead to the following document – *Guidance for Industry: Botanical Drug Products*.²⁰ This document was being distributed for comment purposes only and was therefore not yet the official Regulatory Guidance in May 2004 when this research was completed. The following issues regarding the FDA’s proposed guidelines on herbal products seemed to emerge from this document.

Product validation – As far as product validation was concerned, when submitting an investigational new drug application, the FDA did not insist that the active constituents of the botanical drug be identified, but the identity, quality and consistency of the botanical drugs needed validation. If a botanical drug product showed promise of efficacy, expanded clinical trials of safety and efficacy as well as product quality and consistency was needed (Act 21 CFR 312.b).

Informed Consent – As far as the FDA’s requirements with respect to Informed Consent is concerned, appropriate human research subject protections should be followed and proper informed consent should be received although it was noted that most conditions that are treated by botanical drugs are generally only mildly symptomatic (Act 21 CFR parts 56 & 50).

Safety data - The FDA guidelines state that as long as there are no known safety issues associated with the product and it is used at approximately the same dose that has been used traditionally toxicological data is not needed to initiate a clinical trial. The FDA further recommends that where results of pre-clinical testing are not available, sufficient information from historical sources supporting the clinical study may be used. For example, for this purpose the GRAS (Generally Recognized As Safe) list states the name of natural products that have been traditionally used and are therefore exempt from toxicological testing requirements.



Dosage form - Although no detailed specifications are given regarding the dosage form, it is stated that a single batch or source of product must be used as this is the best way to eliminate any possible product differences or batch variations during the clinical trial. It is generally implied that the dose to be used would correspond with that used traditionally.

Ethics issues – Finally, as with any clinical study, the FDA considers the submission of the protocol to an institutional review board (IRB) as compulsory.

In summary, the conclusion that can be drawn from the mentioned documents is that on the issues of informed consent and ethics, the general guidelines for clinical trials apply.

The FDA did, however, see the need for regulations on herbal medicines and therefore have specific guidelines as far as product validation, dosage forms and safety data are concerned. The FDA is one of the few agencies that specify that the historical use of herbal medicines indicates their safety and therefore does not insist on pre-clinical tests such as toxicological studies for the approval of a clinical trial on herbal medicine.

5.1.2 World Health Organization

The homepage of the website www.who.int was searched using the following terms:

guidelines traditional medicine and the following address was found:

www.who.int/medicines/library/trm/guidelinesdocs.shtml. From this site a 75 page World

Health Organisation document with the following title: *General Guidelines for*

*Methodologies on Research and Evaluation of Traditional Medicine*²¹ was found. When

the document was analyzed for the five main areas the following findings were obtained.

Product validation – The WHO document confirms that the first stage in assuring the quality, safety and efficacy of herbal medicines is the identification of the plant species and as a consequence necessitating the botanical verification of the medicine. In addition the WHO, in another document, *WHO Consultation on Traditional Medicine- Annex III* (September 1990) addressed the issues of quality control, safety and efficacy of herbal medicine (Annex III).

Informed Consent – According to the WHO, the clinical trial must follow a protocol that includes the obtainment of informed consent given by subjects and that has the efficacy

end points well defined. The source of the patients under study should also be comprehensively described along with details of the recruitment process. Any potential bias in patient selection should be excluded.

Safety data - In the WHO guidelines the evaluation of safety is not necessarily the main focus for clinical research on herbal products. Apparently the uneventful use of substances can usually be taken as testimony of its safety and the evaluation of historical literature on its use can give an indication of its potential toxicity. If the traditional use has however not yet been established or adequately documented, appropriate clinical evidence is required. The WHO states that the testing requirements for traditional herbal medicines are not the same as that for new drugs, because traditional herbal medicine have been used by humans for centuries and this may be taken as proof of time-tested usage.

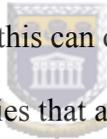


Dosage form - The WHO states that new preparative methods may alter the chemical, toxicological and even pharmacological profiles of tradition herbal medicines and that the dosage form of the herbal product therefore plays a very important role in any submission for a clinical study. The WHO further states that the dose to be used in any study should be based on information indicated by the relevant literature and experience of traditional medical practitioners. However, the WHO indicates that the number of treatments in a finite period of time needs to be clearly stated and that an appropriate time course to demonstrate effectiveness of the treatment, must be allowed.

Ethics issues – The WHO requires that the international ethical guidelines set for biomedical research involving human subjects should be implemented in each clinical

trial for herbal medicine. Further, conventional concepts of clinical research design as described in the Guidelines for Good Clinical Practice (GCP) should be incorporated. In addition, the protocol must be submitted to the regulatory authorities and the study design should include information on the following: number of patients; specific diagnosis; dosage of treatment; duration of treatment; criteria for evaluation (e.g. improvement of symptoms); concomitant treatment; valid statistical evaluation and the target population.

From the guidelines it is apparent that the WHO and FDA are more or less in agreement as far as clinical trials on herbal medicines are concerned. The study population is, however, also addressed by the WHO guidelines. Finally, the WHO particularly pleads for clinical trials on herbal products to establish a place for traditional herbal remedies in the health care system and believes that this can only happen if recommendations for the use of herbal products are based on studies that are credible and acceptable.



5.1.3 Therapeutic Goods Administration (TGA) – Australia

In Australia, the [Australian Health Ethics Committee \(AHEC\)](#) is a principal committee of the National Health and Medical Research Council (NHMRC) that was established under the NHMRC Act 1992. This Act sets out the AHEC's functions, which are to advise NHMRC on ethical issues relating to health and the development of guidelines for the conduct of medical research involving humans. In order to conduct a clinical trial on human subjects in Australia, approval by the Therapeutic Goods Administration (TGA) is needed, but there is no requirement for clinical trials to be done on complementary medicines before an application for registration is submitted. To obtain information on

how Australia handles clinical trials on herbal medicine the following procedure was followed: the search engine *Google* was consulted and the Australian government website was found at the address www.fed.gov.au. When the search words *medical* and *health* were entered, the following site was found – www.nhmrc.gov.au. On the latter site clinical trials are discussed under the topic Ethical Issues. The Australian guidelines (TGA) on complementary medicines are found in the *Australian Regulatory Guidelines for Complementary Medicines*²² (ARGCM). ARGCM Part I discussed the registration of complementary medicines and ARGCM Part III the evaluation of complementary medicine substances. These two sources have the following to say on the five issues under discussion in this project.

Product validation – The TGA accepts that if a traditional medicine has been approved by the United State’s Food and Drug Administration (FDA) as being of “Generally Recognized As Safe” (GRAS) status, the need for further evaluation in Australia will be reduced. However, no specific mention is made regarding the product quality and identity in this document.

Informed Consent – According to the TGA before research is undertaken, the consent of the participants must be obtained. The ethical and legal requirements for consent have two aspects: the provision of information and the capacity to make a voluntary choice. So to conform with the ethical and legal requirements, obtaining consent involves: (i) the provision to participants, at their level of comprehension, of information about the purpose, methods, demands, risks, inconveniences, discomforts, and possible outcomes

of the research; and (ii) the exercise of a voluntary choice to participate by the participant.

Safety data – The TGA insists that for the establishment of safety of a traditional medicine, sufficient numbers of people must have been treated or otherwise exposed to the substance, or to products containing the substance. Where there is sufficient evidence based on human experience to support its safety and if the substance under review is compositionally the same as that used traditionally, other conventional safety studies involving animals and *in vitro* studies will not be necessary. If data documenting human exposure to the substance are deficient, the safety evaluation must be supported by results from other studies (e.g. toxicity studies).

Dosage form – The TGA also requires, like most of the other regulatory agencies, that the dosage, dosage form and route and schedule of administration be indicated in the application. Further, the population and culture in which the traditional use occurred should be clearly identified.

Ethics issues – In Australia the *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) provides the guidelines for the conduct of clinical trials on any therapeutic procedure, including natural or complementary medicines. It states that the aims of every trial must be precisely stated in a protocol presented to and approved by a Human Research Ethics Committee (HREC) and that the HREC, before granting approval to a clinical trial, must be satisfied that the protocol conforms to: (i) the guidelines in the National Statement on Ethical Conduct; (ii) the World Medical Association *Declaration of Helsinki* and where relevant, (iii) the CPMP/ICH *Note for*

Guidance on Good Clinical Practice (CPMP/ICH-135/95); (iv) ISO 14155 *Clinical Investigation of Medical Devices* and (v) the requirements of the TGA.

The Australian guidelines, like that of the FDA and WHO, specifically addresses the product and safety issues of herbal medicines, but the issues of ethics, dosage and informed consent are discussed only in the broader view of clinical trials.

5.1.4 Health Canada

The website: www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/nhp_compliance_policy_e.html was visited and indicated that the *Natural Health Products Regulations*²³ that were implemented in January 2004 could be consulted (this site was forwarded by the supervisor). The guidelines printed in the  Canada Gazette Part II volume 137 no 13 as part of the Food and Drugs Act. Part 4 of the Regulations (pg 55) dealt with the topic of Clinical Trials Involving Human Subjects. These guidelines indicated that all trials should be conducted in accordance with generally accepted principles of *Good Clinical Practice* (see Division 5 of the Food and Drug Regulations). The Canadian regulations dealt with natural health products and clinical trials are dealt with within these regulations. There are therefore no guidelines on clinical trials for natural/alternative medicines as such.

Product validation – According to the Food and Drug Regulations (FDR) of Health Canada, natural health products must be manufactured, packaged, labeled, imported and stored in accordance with the *Good Manufacturing Practice* stipulations. The FDR stated

that the protocol should indicate the physical, chemical and the pharmaceutical properties, if any, of the natural health product. In Canada the regulations stipulate that the known pharmacological properties, pharmacokinetic test results and toxicological effects of the natural health product must be included in the protocol.

Informed Consent - The FDR stipulates that in Canada, like in all the other countries researched, informed consent must be signed and that the procedures followed to obtain consent must be the same as that for all clinical trials involving humans. It is also further stated that the information documents must include the risks and anticipated benefits to the subjects' health that may arise as a result of their participation in the clinical trial.

Safety data – According to the FDR, all the available information regarding the safety, efficacy and dose response of the herbal product that was obtained from previous studies, must be indicated. No specific mention is made in these regulations of information on the historical use of the product being considered as adequate information for safety data.

Dosage form – The FDR specifies that details of the dosage form of the natural health product, the quantity of the ingredient per dosage unit of the product as well as a qualitative list of the non-medicinal ingredients of the product must be included in the protocol.

Ethics issues – To conduct clinical trials on natural health products in Canada, submission for approval must be made to the Research Ethics Board and this committee must include an individual knowledgeable in complementary or alternative health care. It is also mentioned that applications to the ethics committees can be done electronically.

Since the sales in Canada for natural health products are estimated at \$4.3 billion the regulations that were analyzed were intended to provide Canadians with ready access to natural health products that are safe, effective and of high quality, while respecting freedom of choice and philosophical and cultural diversity.²⁴

The remark can be made that the Food and Drug Regulations of Canada are less specific as guidelines for clinical trials on herbal medicines and that the same rules apply for clinical trials as for clinical trials on pharmaceutical products. It was however, interesting to note that the ethics committees that reviewed protocols for clinical trials on herbal medicine had to include a member who is knowledgeable in complimentary/herbal medicine.

5.1.5 Medsafe – New Zealand



Medsafe is the New Zealand Medicines and Medical Devices Safety Authority. It is a business unit of the Ministry of Health and is the authority responsible for the regulation of therapeutic products in New Zealand. Medsafe's mission is to enhance the health of New Zealanders by regulating medicines and medical devices to maximize safety and benefit.

The website for the government of New Zealand was found to be www.govt.nz, but it was difficult to obtain any relevant information from this site. The visited site however revealed that the *New Zealand Guideline for Good Clinical Research Practice*²⁵ was based upon the guidelines used by the EU, UK, Nordic countries, Australia, WHO and the Committee for Proprietary Medicinal Products (CPMP). From the *Guidelines/Codes for Good Clinical Research Practice* it was evident that all research involving human

subjects in New Zealand should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. The *Guidelines for Good Clinical Research Practice (GCRP)* provide the means for ensuring that clinical studies involving human participants are designed and conducted to the highest scientific and ethical standards. These principles are pertinent to all phases and types of clinical investigation involving human participants.

Product validation – Medsafe made no specific mention about herbal or alternative medicine product validations in the GCRP as used in New Zealand.

Informed Consent – The GCRP states that for all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or the permission of a legally authorized representative in accordance with the applicable law.



Safety data – According to the GCRP the protocol must include a summary of all previous studies on the herbal product, including unpublished studies known to the investigators and sponsors. The GCRP states further that all the information on previously published research on the product, including the nature, extent and relevance of animal studies and other pre-clinical studies must be included in the protocol. Unlike the guidelines from the FDA, WHO and ARGCM, no mention is made by Medsafe that information on historical use of natural products being considered sufficient for safety data.

Dosage form - The GCRP clearly states that the description and explanation of all interventions such as the method of treatment administration, route of administration,

dose, dose interval and treatment period for the investigational and comparator products used, must be discussed in the protocol.

Ethics issues – As far as the ethical issues are concerned, GCRP only stipulates that the protocol should be scientifically and ethically appraised by one or more suitably constituted review bodies, independent of the investigators. The GCRP does not specifically address ethical issues pertaining to clinical trials on herbal medicines, but states that all proposals to conduct research involving human subjects must be submitted to one or more scientific review and ethical review committees for review of their scientific merit and ethical acceptability.

In summary, the *Guidelines for Good Clinical Research Practice (GCRP)* of New Zealand does not address any specific issues on herbal medicines or clinical trials on herbal medicines, but only states that all research involving human participants should follow the general guidelines as used for pharmaceutical clinical studies.



5.1.6 The Council of the European Union

Results from the Internet were obtained by the following searches: www.ich.org and a search done for the term: *guidelines*. The website www.emea.eu.int was consulted and searches done on the following terms: *herbal medicinal products*. A diagram of the search followed is set below:



From the above-mentioned sites information could be obtained by first selecting, under the fast track option, the item **GCP** followed by the topic **Human Medicine**, the title **Herbal Medicinal Products** and, lastly, the selection **CPMP** guidelines. Under the latter guidelines the option **HMPC Rules of Procedure** was selected and information obtained on the Committee for Herbal Medicinal Products where the following document could be found: *Note for guidance on specifications: Test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products.*²⁶ (Formerly CPMP/HMPWP/19/99) July 2001. These guidelines however, only discussed

the quality control of herbal medicinal product preparations and contained no information on clinical trials done on herbal medicines. It was however, suggested in this document, that a Committee for Herbal Medicinal Products be established within the European Agency for the Evaluation of Medicinal Products. It was anticipated that this committee would to be active by 2005 and it was stipulated that the aim of this committee was to set out clear standards for the safety and quality of over-the-counter traditional herbal medicines.

A reference was also made to the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 that, in particular Article 1(3), Article 13(1) and Article 15(5) thereof, deals with the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Recommendations for the guidelines in the Directive 2001/20/EC were taken from the US Agency for Health Care Policy and Research (AHCPR, 1994), the WHO General Guidelines and the Therapeutic Goods Administration, Australia. The documents were analyzed for information on the five issues under discussion and the findings are given in the following summary:

Product validation - On product validation issues the HMPC guidelines stated that consistent quality of the products of herbal origin can only be assured if the starting plant materials are defined in a rigorous and detailed manner. According to the HMPC guidelines the characterization of the herbal medicinal products and a detailed evaluation of the botanical and phytochemical aspects of the plant are essential. The guidelines

further advised that the product preparation process should follow the guidelines as set in the guidelines for *Good Agriculture Practice* and *Good Manufacturing Practice*.

Informed consent - Article 3(1) of Directive 2001/20/EC states that in conducting clinical trials on investigational medicinal products for human use, the safety and the protection of the rights of trial subjects should be ensured. It is thus the duty of the Member States to protect individuals who are incapable of giving their informed consent from abuse, including individuals that are temporarily incapable of giving their informed consent, i.e. in emergency situations. The Council states in the mentioned Directive that the process to obtain informed consent from participants must be similar to that followed for all pharmaceutical clinical trials.

Safety data - The Directive 2001/83/EC of the Council of the European Union states that expert evidence on the medicinal use of herbal products throughout a period of at least 30 years may be supplied to supported safety data. It is further stated that pre-clinical tests are not necessary as long as the information on its traditional use proves that the product is not harmful in specified conditions. However, the Directive admits that even a long tradition of use does not exclude the possibility that there may be concerns with regard to the product's safety, and therefore the competent authorities should be entitled to ask for all data necessary for assessing the safety.

Dosage form – The HMPC guidelines on *Test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products* made no specific mention on the dosage form of the herbal product.

Ethics issues - Directive 2001/20/EC Article 3 indicates that all clinical trials shall be conducted in accordance with the ethical principles laid down in the Ethical Principles for

Medical Research Involving Human Subjects that are reflected in World Medical Association Declaration of Helsinki (1996). This is also the basis on which all clinical trials are done in the other countries, but no specific guidelines are given on ethical approval for clinical trials on herbal medicines.

In addition to the afore-mentioned websites, another site, www.mhra.gov.uk i.e. the site of the Medicines and Healthcare Products Regulatory Agency in Britain²⁷ – was also searched but it did not produce any more information other than that which the Ad Hoc Working group (recommended by the Directive as mentioned earlier) intended to work on. The MHRA site did however provide a very useful algorithm (see Table 1) that could be used to determine whether a clinical trial is required for any product under investigation – even herbal products. Following the algorithm it is clear that clinical trials are required for herbal products being tested on humans.



In summary the formulation of any EU guidelines on clinical trials on herbal products has the added challenge of having to harmonize the practices of different member countries. Currently this process is still very much underway. While it can be argued that WHO may be similarly challenged it nevertheless already had more specific guidelines than the Council of the EU. One can thus anticipate that the EU would similarly, also reach such a point in the near future.

Table 1: Algorithm to determine necessity for clinical trial.

IS IT A CLINICAL TRIAL?

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the attached notes. If you have doubts about the answer to any of the questions contact the clinical trials unit at MHRA ☎ 0207 084 2327

A	B	C	D	E	
If you answer yes to any of the questions below go to column B. If you answer no to all these questions, the activity is not a clinical trial.	If you answer no to the question below go to column C. If you answer yes to this question the activity is not a clinical trial.	If you answer yes to any of the questions below go to column D. If you answer no to all these questions the activity is not a clinical trial.	If you answer yes to any of the questions below go to column E. If you answer no to both these questions the activity is not a clinical trial.	If you answer yes to any of the questions the activity is a clinical trial. If you answer no to all these questions the activity is not a clinical trial.	
Is it a medicinal product?	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?	
Are you administering a substance ¹ to a human subject?	Are you only administering any of the following substances? <ul style="list-style-type: none"> • Human whole blood; • Human blood cells; • Human plasma; • Tissues except a somatic cell therapy medicinal product²; • A food product³ (including dietary supplements) not presented as a medicine; • A cosmetic product⁴ • A medical device 	To discover its clinical effects?	To ascertain the efficacy ⁵ of the medicine?	Is the prescription of the medicine linked to the decision to include the patient in the study?	
Is the substance presented as a medicine? i.e. for preventing or treating disease		To discover its pharmacological effects?	To ascertain the safety of the medicine?	Is the medicine prescribed in a manner outside the terms of the marketing authorisation?	
Does the substance function as a medicine? ⁶ i.e. can it be administered, with a view to making a medical diagnosis, to restore, correct or modify physiological functions in human beings or is otherwise administered for a medicinal purpose?			To discover its pharmacodynamic effects?		Does the protocol specify when the patient will take the medicine
Is it an active substance in a pharmaceutical form?			To identify its adverse reactions?		Is any diagnostic or monitoring procedure added to the patients' usual therapeutic strategy?
Is the substance an ingredient in the preparation of a combination of substances administered for a medicinal purpose?					
Is it being used for a medicinal purpose?			To study its absorption, distribution, metabolism or excretion?		Will methods <u>other than</u> epidemiological methods be used to analyse the collected data

5.1.7 The Medicines Control Council (MCC) - South Africa

The guidelines of the final regulatory authority that was assessed in this study was that of the MCC. First, the site for the Department of Health of South Africa could be found using the *Google* search engine. The www.doh.gov.za home page provided one the option to get to the official Documents where the Policy menu gave a selection of guidelines that were arranged in date order according to the year in which they were published and showed the *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa*²⁸ was approved in 2000.

The South African *Guidelines for Good Clinical Practice* focused on the management and regulation of drug trials conducted in human subjects and are based on the following international guideline standards: the Declaration of Helsinki (see Appendix); the International Conference of Harmonization (ICH); Council for International Organizations of Medical Sciences (CIOMS); WHO and the guidelines of Medsafe.

The afore-mentioned South African *Guidelines for Good Clinical Practice* (GCP) document stated that although the guidelines do not specifically address clinical trials on complementary and traditional medicines, the guidelines are such that, in the absence of alternatives, the basic principles outlined in the guidelines may be used to guide any research involving human subjects. Further, it stated the following with respect to the criteria which formed the focus of this investigation.

Product validation – There was no information regarding herbal medicinal products in the Good Clinical Practice guidelines.

Informed consent – Based on the GCP guidelines, the MCC required that informed consent be obtained from subjects and this implied the provision of information on the nature of the research procedure, the scientific purpose and the availability of all alternatives be made known to potential study participants. Furthermore, in South Africa, all this must be achieved via the use of culturally acceptable practices particularly including the use of the participant's home language since the country has eleven official languages. The conditions under which the consent is granted must also be free of coercion, undue influence or incentives. According to the guidelines treatment for a given condition, which might be an attribute of the clinical trial design, should also not be denied when there is refusal to participate.



Safety data – As far as the need for safety data is concerned the guidelines as set up by the MCC do not make any recommendations with reference to the testing of herbal products and the issue regarding safety data necessary for clinical trials on herbal products was not addressed

Dosage form - The dosage form requirements set for herbal products to be investigated in humans were also not discussed.

Ethics issues – The MCC states that all medical research involving human participants must undergo an independent ethical review. Further, an autonomous accredited ethics committee must ascertain that the protection of the participant is assured during the evaluation of a submitted clinical trial application. Moreover, all clinical trials involving either non-registered medicinal substances or new indications for registered medicinal

substances must be reviewed by the MCC. The MCC indeed states that it has a statutory obligation towards the public to ensure that the drugs available in the country fulfil the necessary requirements for safety, quality and efficacy.

From the above it was clear that even though an estimated seventy percent of the population currently uses some form of herbal or natural product, the *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa* did not specifically address the issue of clinical trials on herbal medicines, but at the same time, if regarded as non-registered medicinal substances, did not exclude such trials from their MCC consideration.



Taken together, the first overall conclusion that may be drawn from the information gathered in the Internet and library search of all the internationally available guidelines (i.e. those reviewed above), is that the different countries have different views on the highlighted issues pertaining to clinical trials done on herbal medicine. The FDA, WHO, TGA and FDR (Canada) basically adjusted their existing guidelines for clinical trials on pharmaceutical medicine to accommodate trials on herbal/alternative medicines, while the European Union is still investigating their guidelines and will only implement guidelines specific for herbal medicine in October 2005. On the other hand, New Zealand and South Africa did not have guidelines specific for the testing of herbal products nor did they indicate that they are in the process of adjusting their guidelines to include traditional/herbal products.

The second major conclusion that can be drawn was that the use of a combination of the guidelines given by the FDA, WHO, TGA and FDR would cover all the main issues pertinent for clinical trials of herbal medicines. For example, the FDA, WHO, TGA and FDR, in my opinion adequately addressed the issues of product validation and safety data, while the FDA guidelines covered the issue of the dosage form of herbal medicines and the WHO and TGA provided plausible recommendations on the ethical review of the study and the study population, respectively. The European Union on the other hand only discussed the issues of product validation and the safety of herbal medicines and it seems that New Zealand and South Africa are lagging far behind all the aforementioned countries or agencies in the area of clinical trials on herbal medicines.

A summary of the five issues discussed for the seven international regulatory authorities are given in Table 2.



Table: 2.

**PERTINENT INFORMATION ON SPECIFIC ASPECTS OF HERBAL MEDICINES AND CLINICAL TRIALS ON
HERBAL MEDICINE FROM SELECTED REGULATORY AUTHORITIES**

Agency	Relevant Document	Regulatory Agency's or Institution's Views on issues of				
		Product Validation	Safety Data	Informed Consent	Dosage Form	Ethics Issues
FDA	Guidance for Industry: Botanical Drug Products*	Individual active constituent need not be identified Product identity, quality, consistency need validation	Historical use sufficient for safety data	Addressed specifically in document CFR Act 21 Although symptoms treated with herbal medicine usually mild, informed consent is needed	Single source & batch of the herbal product to be used.	Requirements same as for pharmaceutical clinical trials
WHO	General guidelines for Evaluation of Traditional Medicine*	Addressed in the document Consultation on Traditional Medicine* Botanical verification of the product needed	Information of historical use regarded as testimony of safety	Requirements same as for pharmaceutical clinical trials	Dose of product as indicated by literature of traditional use	Requirements same as for pharmaceutical clinical trials
TGA	ARGCM Part I & III*	Not specifically mentioned but if the product is on GRAS list, reduced evaluation requirements exist	Information on historical use reduce conventional safety testing	Requirements same as for pharmaceutical clinical trials Population & culture to be identified	Dose, dosage form & route of herbal product to be clearly indicated	Requirements same as for pharmaceutical clinical trials

Health Canada	FDR	<i>*Good Manufacturing Practice</i> guidelines to be followed for product validation	Safety, efficacy, and dose response from previous studies to be indicated	Requirements same as for pharmaceutical clinical trials	Quantity of ingredient per dosage unit & qualitative list of non-medical ingredients to be stated	Requirements same as for pharmaceutical clinical trials but IRB committee must include member knowledgeable in herbal medicine
Medsafe	GCRP	No specific guidelines for product validation	Previous clinical & pre-clinical safety data needed	Same procedure as for pharmaceutical clinical trials	Dose, intervals, route & treatment period to be included in protocol	Requirements same as for pharmaceutical clinical trials
EU	HMPC & Directive 2001/83/EC	Detailed evaluation of botanical & phyto-chemical aspects essential as described in the <i>Good Manufacturing Practice*</i> document	Same procedure as for pharmaceutical clinical trials Addressed in the <i>Directive 2001/20/EC</i> document	Information on historical use of minimum 30 years to support safety data as indicated in <i>Directive 2001/83/EU*</i> document	<i>Test procedures & acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal product*</i> document	Requirements same as for pharmaceutical clinical trials
MCC	GCP	No specifications on product validation for herbal products given	Requirements same as for pharmaceutical clinical trials, within culturally acceptable practices e.g. own language	No specific mention made regarding safety data	No guidelines regarding dosage forms of herbal medicine available	Requirements same as for pharmaceutical clinical trials

* for websites see sections 5.1.1 to 5.1.7

5.2 RESULTS OF SEARCH ON CLINICAL TRIALS ON HERBAL MEDICINE AND SPECIFICALLY HERBAL ANTI-ASTHMA TREATMENTS.

The extensive search on the literature for clinical trials on herbal medicines lead to many review articles, abstracts and web pages that generally revealed that by the middle of 2003 more than 5000 clinical trials had been done on alternative medicine. Of these only 258 (5.2 %) however met all the inclusion criteria as set by the National Centre for Complementary and Alternative Medicine (NCCAM). In fact, the evaluation of 2938 Randomized Clinical Trials on Chinese medicines showed them to have major trial design defects.²⁹



For the present study the information on the Internet-based literature was obtained by searching the Medline, Pubmed, Cochrane Library and Embase databases using the following search terms: *asthma herbal traditional medicine clinical trials*. By July 2003 (when this search was conducted) at least seventeen randomized clinical trials had been done on herbal treatments for asthmatic patients. Six were done on Chinese herbal medicine, eight on Indian medicine and three on Japanese traditional medicine. The endpoint measures used in these studies included lung functions tests, symptom scores and diaries. In terms of outcomes a clinical relevant improvement of lung function and/or improvement of symptom scores were obtained in nine of the reported trials. In many cases the clinical trials showed positive outcomes with clinically relevant increases in lung function measured and controls used included inhaled steroids. Relatively large

subject numbers were used and the duration of the trials varied from two hours to six months. All the trials were rated according to methodological rigor using the Jadad score as explained in Table 3.³⁰ In this system, the studies are rated based on criteria dealing with study randomization, blinding and withdrawals and dropouts. The most correct study would be given a score of 5.

Table 3

JADAD SCORE SYSTEM

Scoring system to measure the likelihood of bias as described by Jadad.

-
1. Study described as randomized (this includes the use of words such as "random", "randomly" and "randomization")?
 2. Study described as double blind?
 3. Description of withdrawals and dropouts?
 4. Method to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc)?
 5. Method of double blinding described and appropriate (identical placebo, active placebo, dummy etc)?
 6. Method to generate the sequence of randomization described and inappropriate (patients were allocated alternately or according to their date of birth, hospital number, etc).
 7. Method of double blinding described and inappropriate (e.g. comparison of tablet vs. injection with no double dummy).
-

For questions 1-5 Yes = 1 point and No = 0 points. Deduct 1 point if questions 6 or 7 apply.

The relevant information of the references and study detail for the different trials on Chinese, Indian and other herbal treatments were scored using the Jadad system and summaries of the results given in table 4.1, 4.2 and 4.3.³¹

**PERTINENT INFORMATION ON SPECIFICATIONS OF HERBAL
MEDICINES AND CLINICAL TRIALS ON HERBAL MEDICINE**

Table 4.1 (taken from reference 31)

Chinese traditional medicine and asthma

<i>Reference</i>	<i>No, definition, duration of trial</i>	<i>Treatment (n)</i>	<i>Control (n)</i>	<i>Primary measures</i>	<i>Results</i>	<i>Jadad score</i>
Li <i>et al</i> ⁴	61 asthmatics, 8 weeks	Ginkgo leaf liquor (39)	Placebo (22)	Lung function tests	Clinically relevant increase in FEV ₁ at 8 weeks (p<0.05), significantly greater than control (p<0.05)	1
Shao <i>et al</i> ⁵	150 bronchial asthmatics (moderate to severe), 1 month	<i>L wallichii</i> mixture (100)	Control tea (50)	Lung function tests; subjective symptoms	Increase in FEV ₁ with treatment but not clinically significant. Improvement in subjective symptoms with treatment but no criteria or statistics	1
Xu <i>et al</i> ⁶	117 cold and heat type asthmatics, 2 weeks	SBR decoction (58)	Control herbal tea (59)	Lung function tests	Increase in FEV ₁ with treatment but not clinically relevant	1
Xu <i>et al</i> ⁷	41 severe asthmatics, 4-6 months	RKISP decoction and steroid aerosol (21)	Steroid aerosol (20)	Lung function tests	Clinically relevant increase in FEV ₁ (p<0.05) but not greater than control	1
Xu and Xu ⁸	57 seasonal asthmatics, 3 months	IKPA tablets and inhaled BDP (32)	Inhaled BDP only (25)	Lung function tests	Clinically relevant increase in FEV ₁ with treatment (p<0.001), significantly greater than control (p<0.05)	1
Zou <i>et al</i> ⁹	68 asthmatics of 'cold type', 8 weeks	Wenyang Tonglulo mixture (34)	Oral salbutamol and aerosol BCP (34)	Lung function tests	Clinically relevant increase in FEV ₁ with treatment (p<0.05), significantly greater than control (p<0.05)	1

SBR = strengthening body resistance; IKPA = invigorating kidney for preventing asthma; RKISP = reinforcing kidney and invigorating spleen principle; FEV₁= forced expiratory volume in one second; BCP = beclomethasone dipropionate.

Table 4.2 (taken from reference 31)

Traditional Indian medicine and asthma

Reference	No, definition, duration of trial	Treatment (n)	Control (n)	Primary measures	Results	Jadad score
Doshi <i>et al</i> ¹⁰	72 bronchial asthmatics, 14 weeks	2 wks of placebo followed by 12 weeks of <i>P kurroa</i> (24)	(a) 2 wks placebo, 3 wks <i>P kurroa</i> , 9 wks placebo (26) (b) 2 wks placebo, 3-6 wks <i>P kurroa</i> , 9-12 wks placebo (22)	Lung function tests; diary	No significant differences between treatment and placebo	3
Govindan <i>et al</i> ¹¹	60 bronchial asthmatics, 2 hours	<i>S xanthocarpum</i> (20) or <i>S trilobatum</i> (20)	Salbutamol (10) or deriphylline (10)	Lung function tests	Significant increase in FEV ₁ in both herb preparation groups (p≤0.01) but less than standard drugs	1
Gupta <i>et al</i> ¹⁸	135 bronchial asthmatics, 3 weeks	Powdered <i>T indica</i> (71)	Powdered placebo (64)	Lung function tests; symptom score	No differences between treatment and placebo	4
Gupta <i>et al</i> ¹³	80 bronchial asthmatics, 6 weeks	Encapsulated powdered <i>B serrata</i> gum resin (40)	Encapsulated lactose (40)	Lung function tests	FEV ₁ significantly increased with treatment vs. control (p<0.0001) but % increase could not be calculated from data given	2
Mathew and Shivpuri ¹⁶	123 bronchial asthmatics, 12 weeks	Alkaloid extract from <i>T indica</i> in glucose	Glucose coloured with spinach	Lung function tests; symptom score	% patients with >15% increase in FEV ₁ : test > control at all times peaking at 4 wks (p<0.01); symptom score: test > control at all times (p<0.05)	4
Shivpuri <i>et al</i> ¹⁴	110 bronchial asthmatics, 12 weeks	<i>T indica</i> leaves chewed and swallowed (53)	Spinach leaves chewed and swallowed (57)	Daily diary	Symptom relief at 6 days: test 62%, control 28%; at 12 wks: test 16%, control 0% (no statistics)	2

Reference	No, definition, duration of trial	Treatment (n)	Control (n)	Primary measures	Results	Jadad score
Shivpuri <i>et al</i> ¹⁵	195 bronchial asthmatics, 12 weeks	<i>T indica</i> powder (179)	Placebo powder (166)	Diary of symptom scores	Complete to moderate relief at 1 wk: test 56%, control 31% (p=0.01), 12 wk: test 14.8%, placebo 7.8% (NS)	3
Thiruvengadam <i>et al</i> ¹⁷	30 bronchial asthmatics, 16 days	(a) <i>T indica</i> /7 days, 2 day break, placebo/7 days (b) placebo/7 days, 2 day break, <i>T indica</i> /7 days	(c) <i>T indica</i> /7 days, 2 day break, standard drugs/7 days (d) standard drugs/7 days, 2 day break, <i>T indica</i> /7 days	Lung function tests; symptom score	No statistics given for lung function; nocturnal dyspnoea significantly better with <i>T indica</i> than placebo (p<0.01)	3

Table 4.3 (taken from reference 31)

Other herbal treatments and asthma



Reference	No, definition, duration of trial	Treatment (n)	Control (n)	Primary measures	Results	Jadad score
Egashiri and Nagano ²⁰	112 steroid dependent bronchial asthmatics, 12 weeks	TJ-96 plus conventional drugs (64)	Conventional drugs only (48)	Lung function tests; symptom diary	No data given on lung function; symptom improvement and perceptions greater in test than control group (p<0.01)	2
Taskin <i>et al</i> ²⁴	10 bronchial asthmatics (stable to moderate) defined by ATS criteria, 2 hours	(a) Smoking marihuana (2% THC), (10) (b) Ingestion of 2% THC capsules (10)	(a) Smoking marihuana (0% THC), (10) (b) Ingestion of placebo capsules (10)	Lung function tests	Smoking and ingestion of marihuana resulted in lower Raw but not clinically relevant	3
Mansfeld <i>et al</i> ²⁵	24 bronchial asthmatics, 3 days	Dried ivy extract (24)	Placebo (24)	Lung function tests	Raw significantly better with ivy extract (23.6%) vs. placebo (p=0.0361)	4

THC = tetrahydrocannabinol; Raw = airway resistance.

Based on the analysis of Huntley and Ernst the overall the quality of these trials with anti-asthmatic treatments were very poor mainly due to methodological imperfections of the trials and 14 of the 17 trials scored 3 or less on the Jadad score system. The relevant weaknesses were:

5 of the trials included children as well as adults; 3 of the trial designs did not state age ranges; in all 17 trials no statistical sample sizes were calculated; only one trial described the method of randomization; withdrawals and exclusions were mentioned in only 2 papers; 8 of the trials were not double-blind and the quality of the herbal products was not standardized. (It must however be noted that since these were more research articles rather than full final reports of clinical studies, some of the pertinent information may not have been given but could still be available in the full study reports of the abovementioned trials.)



Although the results for some of the trials indicated a possible value of the herbal medicine in the treatment of asthmatics, the trial design/methods showed significant imperfections and therefore no convincing overall conclusions could be drawn on that point. There were however also studies with promising results that warrant further research and analysis.

The search did not indicate that, by 2003, trials had been done on any African traditional anti-asthmatic medicine.

Overall the brief search suggested that the guidelines (i.e. of WHO, FDA, etc) for the conduct of clinical trials were not followed and therefore the quality of the clinical trials on herbal medicines was generally inferior to the clinical trials done on regular pharmaceutical products.

Nevertheless the results of the search of the international guidelines for clinical trials on herbal medicines and the trials that have been done previously on herbal medicines, suggested that a viable protocol that focuses on the study objective, methodology, informed consent and ethical approval, could be successfully set up, provided the following issues were correctly addressed: The clinical trial should definitely be randomized and blinded; the duration and outcome of the trial should be scientifically relevant; the dose of the herbal product should be in the same form as used traditionally and the product validated; all information on the historical use of the herbal medicine and any available safety data should be included in the protocol; it was also crucial that the inclusion and exclusion criteria be very precise, the study population specified and the informed consent fully detailed. The statistical analysis must be accurate and fully comply with the international standards and finally the approval by the regulatory and ethical authorities would ensure the clinical trial the same prestige that most clinical trials on regular pharmaceutical products are awarded.

5.3 THE DESIGN OF THE SAMPLE STUDY – THE SMARt TRIAL

Following the above-mentioned guidelines, a protocol was designed for the testing of the herbal medicine *Artemisia afra* in mild to moderate asthmatic subjects. The full protocol that was designed is given in Appendix 1 and the synopsis in Table 5. The important issues features indicated by the various guidelines and included in the protocol can be summarized as follows:

- The protocol clearly stated the objective of the clinical trial.
- A detailed plan regarding the methodology, statistical consideration and organization of the trial was given.
- Appropriate provision was made to adequately inform subjects of the aims, methods, sources of funding, potential hazards/discomforts it may entail and the freedom to withdraw consent by means of the Patient Information Leaflet and Consent Form.

Table: 5.

PROTOCOL SYNOPSIS	
Title:	SMArt Study – A Pilot Study on Mild to Moderate Asthmatics subjects to test the bronchodilatory effect of the herbal medicine, <i>Artemisia afra</i> in two Phases.
Investigational site:	Health Care Centre, University of the Western Cape, Bellville, Cape Town
Investigators:	Prof P Mugabo, Prof James Syce, Dr M Bagwandeem
Study number:	UWC 001
Final Protocol:	September 2003
Ethics Approval:	October 2003
Clinical Phase:	January to September 2004
Statistical analysis:	Phase A: July 2004 Phase B: November 2004
Background:	Asthma is a condition for which plant medicines and traditional remedies have frequently been advocated as treatment. The validity of claims of effectiveness made for the plant <i>Artemisia afra</i> , need to be investigated.
Objective:	To assess the bronchodilator response of a <i>Artemisia afra</i> broth compared to placebo in patients with stable asthma firstly in tea/broth form and then in a tablet form.
Trial Phase:	Therapeutic exploratory/ Phase II
Test Product, Dose and mode of administration:	<i>Artemisia afra</i> as obtained from traditional medicine suppliers in South Africa, 2 teaspoons dried leaf product brewed in 200 ml boiled water taken twice daily for 12 weeks for Phase A and 1 tablet of <i>Artemisia afra</i> twice daily for 12 weeks in Phase B.
Placebo:	2 teaspoons Rooibos tea (caffeine free) brewed in 200 ml boiled water administered as a tea taken twice daily for 12 weeks in Phase A and 1 tablet Rooibos twice daily for 12 weeks in Phase B.
Methodology:	A 24 week, randomised, single blind, cross-over study to examine efficacy of <i>Artemisia afra</i> versus placebo in subjects with stable asthma with or without maintenance treatment. Patients will also do a daily diary regarding a Peak Flow Volume, symptoms score and need for rescue medication.

Subjects:

Diagnosis: Mild to Moderate Asthmatic patients diagnosed according to ATS Criteria

Inclusion Criteria

- Written Informed Consent
- Outpatients of either sex
- Age 18-60 years
- FEV1 > 80% predicted normal
- No significant concomitant diseases

Exclusion Criteria

- Asthma exacerbation during month prior to study enrolment
- Smoking history of > 10 pack years
- Pregnancy, Breast feeding
- Non-African patients

Duration of study: Twenty- four weeks



Endpoint: Efficacy - FEV1 mean difference from baseline after use of herbal

medicine for 12 weeks

Number of Exacerbations

Reduction in use or dosage of Inhaled Glucocorticosteroids

Safety: Incidence and type of adverse events during study period

Blood levels of flavanoid compounds on the active arm in Phase B.

Statistical analysis: The analysis will be based on data from all patients who were randomized and from whom meaningful data were collected. The primary analysis will be based on the FEV1 measured at baseline and at end of treatment A after week 12 and again at the end of treatment B after week 24.

The sample size of 40 randomized patients was chosen to achieve a power of 80% for concluding efficacy, assuming a mean difference of 255 ml was achieved.

5.4 THE ACCEPTABILITY OF THE SMARt STUDY

To test the acceptability of the protocol it was submitted for regulatory and ethics board (IRB) approval, i.e. to the MCC and two other ethics committees (University of Stellenbosch and PharmaEthics), respectively. In addition the comments from two experts were solicited. It was assumed that approval of the protocol by either the regulatory or ethics authority would be the major measure of acceptability of the study. The results of these processes and the outcomes obtained during the actions are presented below.

5.4.1 Application to the Medicine Control Council of South Africa



The Medicines Control Council of South Africa (MCC) is the regulatory authority in SA. The process for this submission did not present major problems. The website, www.mccza.co.za gave all the necessary information and forms that had to be completed to make an application for approval to this committee. The documents and information needed was given under the heading **Forms** on the aforementioned web address. For the application, twenty-one items of information were needed and had to be set out in the following order:

1. Covering letter.
2. Cover sheet.
3. Checklist.
4. Completed Application form.
5. All documents to be submitted in duplicate with two electronic copies.
6. Additional 25 copies of the application form itself must be submitted.

7. Protocol
8. Patient Information leaflet and Informed consent form
9. Standardized MCC contact details/wording to be added to PILs.
10. Investigators Brochure/Package insert.
11. Signed investigator(s) CV(s) in MCC CVs format.
12. Signed Declaration by Principal investigator(s).
13. Signed joint declaration by Sponsor/National Principal investigator.
14. Signed Provisional declaration by Co- or Sub-investigators
15. Signed Declaration by regional monitor
16. Indemnity and Insurance Certificate and/or
17. Proof of Malpractice insurance of trialist(s).
18. Ethics committee(s) approval or
19. Copy of letter submitted to Ethics committee(s).
20. Diskettes to be submitted in word.
21. Financial declaration

The complete application that was eventually prepared (Appendix 2) included all the information requested and was sent via courier and its receipt by the MCC was confirmed telephonically on 25 September 2003. As far as the Investigators brochure/Package insert was concerned, a copy of all the literature available on the historical use of the plant was included. A notification was made regarding the insurance certificate and ethics approval that was still outstanding at the time of submission to the MCC.

All applications for review at the meeting of 5 November 2003 were due at the MCC by 28 September 2003. The 5 November meeting was however postponed and the response to this effect only received via fax and e-mail on 26 November 2003. The full two-page response received is given in Appendix 2 and included the following details: The MCC Reference No, Status, Applicant, Medicine investigated, Protocol number of the study, the title of the study and their Clinical Trial Committee (CTC) recommendation. The letter stated that the study was not approved on account of the following issues:

1. No safety data has been submitted and the pharmacokinetics of the drug was to be addressed.
2. It was recommended that patients' chests be X-rayed to exclude other pathologies in the chest.
3. The question was asked whether patients should not have blood tests for exclusion purposes.
4. Safety monitoring was apparently not addressed.
5. Question 13 of the MCC application was apparently not answered.
6. The issue of insurance was a crucial factor.
7. The Ethics committee approval was to be submitted to MCC.
8. Minimum compensation of R150 per visit to trial subjects was to be adhered to.

(For complete list of recommendations see Appendix 2)



On this letter the study approval was listed as of category 5 (the code indicating that the study was not approved and had to be resubmitted along with a reply to the points highlighted) and, initially, it was not clear what the classification exactly meant. As far as the acceptability was concerned, the MCC pointed to the following issues: The main problem was the lack of safety data, toxicological studies and approval by an ethics committee. In my opinion the other issues (as given in Appendix 3) were of lesser importance, as those questions could be easily answered.

Due to the fact that the summer holidays had started in December, a reply was sent to the MCC during January 2004. The response letter included the MCC reference number, the

applicant and study medication name, the protocol number and name and the full title of the protocol and a copy of the letter is given below.

MCC Ref No: N2/19/8/2 [2027]

STATUS: 8.1.15

APPLICANT: PROF J SYCE

MEDICINE: *Artemisia afra*

PROTOCOL: UWC 001

TITLE: *A pilot study on mild to moderate asthmatic subjects to test the bronchodilatory effect of the herbal plant Artemisia afra.*

Reply on CTC recommendations:

- 2.1 Safety data: No safety data was available for the investigated herbal plant, other than the literature on historical use of the plant for respiratory tract conditions.
- 2.2 X-rays to exclude other pathologies in the chest: Patients will be excluded on a known history of other pulmonary disease and therefore the x-ray of the lungs will not be applicable.
- 2.3 Blood tests for exclusion: No exclusions will be made on abnormal blood results and no testing will be done.
- 2.4 Safety monitoring: Daily diary recordings: symptom scores, use of rescue medication and nocturnal awakenings. Blood levels of flavanoids on a sub-group of subjects on the active treatment arm in Phase B. Physical examination. Adverse Events.
- 2.5 Question 13: See attachment
- 2.6 Insurance: The UWC currently has insurance cover and is in the process of extending this cover for clinical trials. No study procedures will continue until the insurance is granted and the MCC informed about the specifics.
- 2.7 Ethics Committee approval: To be submitted to MCC on receipt of the approval.
- 2.8 Subject compensation: The investigator will adhere to the recommended compensation of R150.00 per visit per patient.

(The attachment was a completed Question 13 that had been omitted by mistake.)

Despite the above reply being forwarded to the MCC, it seemed that the committee could not approve the proposed clinical trial on herbal medicine and no further correspondence was received from the MCC regarding the reply.

Overall, the conclusion was thus drawn that the MCC did not have guidelines or committees in place to approve a study of this nature and reviewed this study as for a trial on a regular pharmaceutical product and required a stronger argument to have it tabled for review or approval. The only major stumbling block appeared to be issue of lack of safety data and perhaps reference should have been made to the FDA and WHO guidelines that allows for the historical use of herbal medicine as adequate safety information.



5.4.2 Application to the ethics committee at the University of Stellenbosch

The submission to the ethics committee of the University of Stellenbosch on 11 February 2004 presented no problems as all the necessary information was obtained from their website: www.sun.ac.za and the necessary forms received via electronic mail. A checklist and CPTO4 form had to accompany the protocol and covering letter and it could be submitted on completion because the committee had meetings on a regular basis. The application (see Appendix 4) was hand delivered and within 20 days - on 3 March 2004 – a three-page response was received via fax (see appendix 5). Generally the committee was in agreement with the project, but could not approve until the 20 issues

identified were addressed. It was clear that the committee had discussed the study in detail and the evaluation was well thought through.

The issues raised by the US ethics committee included the insurance, quality and preparation of the herbal product, the toxicology of flavanoids, baseline blood tests, concomitant medication and specifications of the Patient Information Leaflet. The fact that no more safety data on the use of the herbal plant *Artemisia afra* other than that already included and no toxicology tests of the active ingredient (flavanoids) were available, meant that the protocol could also not be resubmitted to the IRB for approval.

It was thus evident from the response of the above-mentioned ethics committee, that the same issues were problematic for this committee as were for the MCC. Yet again, the main concern was the absence of safety data and toxicological studies. The committee also stated in their letter that it was of the opinion that the proposed study was of importance and that the comments were meant in a positive and constructive manner so that the study could be improved to a do-able level.

Again, the conclusion could be made that the argument, that the World Health Organization accepts historical use of medicinal plants as adequate safety data, should have been strongly put to have the study approved.

5.4.3 Application to PharmaEthics

The specifications for the application to PharmaEthics were obtained via electronic mail and the following information was requested:

- 1.1 Signed & Dated Application Form.
- 1.2 Trial Protocol of the proposed research
- 1.3 Synopsis of the Protocol.
- 1.4 Diary Cards & other Questionnaires intended for research participants.
- 1.5 Proposed English Written Informed Consent Form
- 1.6 Subject recruitment procedures (e.g. *Advertisements*)
- 1.7 Investigator's Brochure / Registered Package Insert / available safety information.
- 1.8 Information about payments & compensation available to subjects & investigators.
- 1.9 Principal & co-/sub-investigator's current *Curriculum Vitae*
- 1.10 Details of Financial Agreements with investigators
- 1.11 A copy of the Sponsor's Insurance Certificate covering the Protocol
- 1.12 Medicines Control Council (MCC) Approval Letter
- 1.13 All significant previous decisions by other EC's or regulatory authorities for the proposed study)
- 1.14 A motivation for the use of a placebo control

The completed application was couriered to PharmaEthics on 21 February 2004.

PharmaEthics had meetings every two weeks to review proposed trials and the response to our application from them was received on 25 March 2004. This ethics committee raised five issues in a two-page response that was received via fax. The impression was however given that the committee did not regard the study of much importance, for

instance no mention was made of the lack of safety data. Their main concerns were as follows: (for complete list see appendix 6)

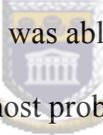
1. The fact that Rooibos tea had medicinal qualities made it an unacceptable placebo.
2. The reduction in the use of rescue medication as a variable in the primary efficacy analysis was addressed.
3. It was highlighted that with the cross over the placebo patients stayed on placebo and did not cross over to active treatment.
4. The standard deviation for determining of sample size was mentioned.
5. A non-African patient was to be defined.

In our response to these issues, made on 29 March 2004, it was suggested that (1) the Rooibos placebo will be replaced as it apparently also has a medicinal effect; (2) the reduction in medication referred to the maintenance medication; (3) the plan diagram was indeed incorrectly labeled; (4) previous studies on pharmaceutical product were used as reference for the statistical analysis and (5) that non-African patients refers to people who would not normally take or believe in traditional herbal medicine. (For complete response see appendix 7)

On 26 April 2004 the PharmaEthics committee faxed their reply (Appendix 8) stating that the study could still not be approved and recommending that a new protocol be submitted. There was also some confusion regarding the reduction of medication as a primary efficacy analysis although it was considered as a study endpoint. According to

the committee the sample size that was based on lung function measurements contradicted the primary efficacy measurement. For all these reasons, the ethics committee could not approve the protocol and recommended that a new protocol be submitted.

Overall the conclusion could be drawn that the PharmaEthics committee was more focused on the scientific correctness of the protocol and highlighted a few legitimate arguments. For this ethics committee the safety data was not the main focus, but still the protocol was not approved.

In summary, neither the MCC nor two ethics committees, (the regulatory or ethics watchdogs in South Africa) respectively,  was able to approve the study as submitted. On one hand it could be argued that it was most probably the first application or submission of its kind in South Africa and the committees did not have the systems and processes in place to properly review such a proposal. On the other hand and in hindsight, it could be argued that the smaller issues could have been sorted out and strong reference should have been made to the WHO and FDA guidelines on historical use to circumvent the issue of lack of safety data.

5.4.4 Acceptability of clinical trial on herbal medicine: Trial subjects views

It was important to test the acceptability of the clinical trial on trial subjects. So to test the public's view on clinical trials on herbal medicine, a small group (19) of subjects, already

acquainted with the procedures of conventional medicine clinical trials, were asked to give their opinion via an informal questionnaire. No trial specific details were given and a copy of the questionnaire that was completed is given in table 6.

Table: 6.

<u>QUESTIONNAIRE FOR CLINICAL TRIALS ON HERBAL MEDICINE</u>													
<p>The information obtained from this questionnaire will be used for research regarding volunteer participation in clinical trials on herbal medicine. The information obtained will be anonymous and in no way reveal any personal information - please give your personal and honest view!</p>													
<ol style="list-style-type: none"> 1. Have you participated in any clinical trials before? 2. Did any of the clinical trials involve herbal products? 3. Do you take any herbal products regularly? 4. Would you take part in clinical trials with herbal products? 5. In your opinion, should trials be done on herbal products and if yes, give your reason why it is necessary. 	<table border="1"> <thead> <tr> <th style="padding: 2px;">Yes</th> <th style="padding: 2px;">No</th> </tr> </thead> <tbody> <tr><td style="height: 20px;"> </td><td style="height: 20px;"> </td></tr> </tbody> </table>	Yes	No										
Yes	No												
<hr style="border: 0; border-top: 1px solid black; margin: 10px 0;"/> <hr style="border: 0; border-top: 1px solid black; margin: 10px 0;"/>													
<p><i>Thank you for your time!</i></p>													

74% of the respondents who completed the questionnaire were willing to take part in a study on herbal medicine and 79% of the respondents were of the opinion that such trials were necessary to secure safe and tested herbal medicine on the market. Another pertinent issue that was raised through the open ended questionnaire was the fact that the side effects of herbal products were not generally known and was therefore another reason why clinical trials on such herbal products should be conducted.

5.4.5 Acceptability of trial on herbal medicine: Clinical Investigators views

Finally the acceptance of trials by clinical investigators was assessed. The professor with years of experience in clinical trials on pharmaceutical medicine was given a protocol for review and asked to comment on the acceptability of the trial on herbal medicine. This professor was of the opinion that trials of this kind were definitely due as hundreds of products are being sold without any clinical evidence of efficacy. He was also of the opinion that the design of the protocol that was developed in this study was of the standard as required by the regulatory and ethical authorities.

The other Clinical Investigator with more than four years experience of clinical trials on pharmaceutical medicine – mostly asthma medication was also of the opinion that the protocol did not show major shortfalls and that the outcome of the trial would be very interesting. Clinical trial monitors and coordinators were also interviewed and the conclusion could be drawn that medical personnel with interest in clinical trials were definitely not unwilling to participate in clinical trials on herbal medicine and that alternative medicine needed clinical investigation to demonstrate efficacy. In their opinion the biggest problem, however, would be funding, as clinical trials of this nature required large budgets.

Overall, the conclusion may be drawn that at least some investigators would find properly designed clinical trials on herbal medicine very acceptable and, in fact, long overdue.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

The WHO estimates that 4 billion people – 80% of the world population – use herbal medicine for some aspect of primary health care.³² The herbal products are however mostly used without the necessary clinical trials having been done to prove their pharmacological activities and, therefore, their quality, efficacy and safety.

Furthermore, of the 50 000 clinical trials currently conducted in the USA, a small percentage are being done on herbal medicine.³³

It was the objectives of this study 1) to review the current international guidelines for the evaluation of herbal medicine; 2) to gain a perspective on the number, type and quality of clinical trials that have been done on herbal medicine and to adopt a set of guidelines that could be used to conduct a trial on a traditional herbal medicine used in South Africa. To verify these guidelines, 3) a protocol for a clinical trial was drafted and submitted for approval to the regulatory and ethical authorities in South Africa. The final objective of this study was 4) to determine the acceptability by clinical investigators and trial subjects of the afore-mentioned drafted clinical trial.

From the results that were obtained the following conclusions could be drawn.

1. There are either no specific guidelines, or else the guidelines for clinical trials on herbal medicines provided by some of the major regulatory agencies in the world, viz. WHO, FDA, EU, Canada, and New Zealand, and South Africa showed some significant differences.

The guidelines for clinical trials on herbal medicines given by the WHO and FDA were more or less in agreement. Nevertheless, these two agencies urged that credible and acceptable studies be done on herbal products in order to establish a place for traditional herbal medicine in the healthcare system. To encourage this, these agencies (and to some extent the TGA) accepted traditional use of herbal products as adequate evidence of their safety.

The other countries under review (Canada, New Zealand, Europe and South Africa) did not have definite guidelines for herbal medicines in place, although they were clear that the same guidelines used for pharmaceutical clinical trials applied for clinical trials done on herbal medicines, as human subjects are involved.



2. Most of the clinical trials that have already been done on herbal medicines had serious shortcomings, particularly related to the methodological quality (i.e. study design and analysis of results) of the studies. Other criticisms included blinding and withdrawals that did not meet the criteria as set for regular pharmaceutical products and the quality of the tested products were not standardized. Even in cases where promising results were suggested it was quite apparent that much further research is needed.

3. The absence of specific guidelines for clinical trials on herbal medicines issued by the MCC significantly hampers the conduct (approval) of clinical trials on herbal medicines that are traditionally used in South Africa.

The MCC definitely did not have systems in place to review the submitted protocol and therefore it could not be approved. If, however the MCC (like the WHO and FDA) accepted historical use of the plant *Artemisia afra* as adequate safety data, the outcome of this study may have been different. As far as the ethics committees were concerned, the conclusion can be drawn that the design of the protocol was a problem for the one committee, the absence of safety data and toxicological studies proofed to be unacceptable for the other.

4. The final major conclusion that may be drawn from the study is that the medical professionals as well as the public seem to be ready and willing to participate in clinical trials on herbal medicine.

Collectively, the above conclusions lead to the recommendations that the MCC should accept the guidelines as set by the WHO and FDA in order to approve clinical studies without the need for stringent safety data and that the reason why clinical trials on herbal medicine are not done in parallel with pharmaceutical products, is the lack of uniform regulatory control in the form of guidelines. It is my opinion that if herbal medicine are tested and proven to be effective, the use of safe and effective traditional medicines will increase and potentially lead to lower healthcare cost and improved public health – a betterment that is much needed in countries like South Africa. To make this possible internationally standardized guidelines for randomized clinical trials on herbal medicines have become essential.

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APPENDIX 1

Complete Protocol: SMArt Study



Clinical Study Protocol
Drug Substance: *Artemisia afra*
Version no: 01
Study code: UWC 001
Date: September 2003

A Pilot study on Mild to Moderate Asthmatic subjects to test the bronchodilatory effect of the herbal plant *Artemisia afra*.



Investigators: Prof Pierre Mogabo, Prof James Syce and Anthea van Wyk

The following amendment have been made to this protocol since the date of preparation:
Amendment No. Date of amendment

PROTOCOL SYNOPSIS

Title: SMARt Study – A Pilot Study on Mild to Moderate Asthmatics subjects to test the Bronchodilatory effect of the herbal medicine, *Artemisia afra* in two Phases.

Investigational site: Department of Pharmacology, University of the Western Cape, Bellville, Cape Town
Investigators: Prof James Syce,
Study number: UWC 001
Final Protocol: September 2003
Ethics Approval: October 2003
Clinical Phase: January to September 2004
Statistical analysis: Phase A: July 2004 Phase B: November 2004

Background: Asthma is a condition for which plant medicines and traditional remedies have frequently been advocated as treatment. The validity of claims of effectiveness made for the plant *Artemisia afra*, need to be investigated.

Objective: To assess the bronchodilator response of a *Artemisia afra* broth compared to placebo in patients with stable asthma firstly in tea/broth form and then in a tablet form.

Trial Phase: Therapeutic exploratory/ Phase II

Test Product, Dose and mode of administration: *Artemisia afra* as obtained from traditional healers in South Africa, 2 teaspoons dried leave product brewed in 200 ml boiled water taken twice daily for 12 weeks for Phase A and 1 tablet of *Artemisia afra* twice daily for 12 weeks in Phase B.

Placebo: 2 teaspoons Rooibos tea (caffeine free) brewed in 200 ml boiled water administered as a tea taken twice daily for 12 weeks in Phase A and 1 tablet Rooibos twice daily for 12 weeks in Phase B.

Methodology: A 24 week, randomised, single blind, cross-over study to examine efficacy of *Artemisia afra* versus placebo in subjects with stable asthma with or without maintenance treatment. Patients will also do a daily diary regarding a Peak Flow Volume, symptoms score and need for rescue medication .

Subjects: Diagnosis

- Mild to Moderate Asthmatic patients diagnosed according to ATS Criteria

Inclusion Criteria

- Written Informed Consent
- Outpatients of either sex
- Age 18-60 years
- FEV1 > 80% predicted normal
- No significant concomitant diseases

Exclusion Criteria

- Asthma exacerbation during month prior to study enrolment
- Smoking history of > 10 pack years
- Pregnancy, Breast feeding
- Non-African patients

Duration of study: Twenty four weeks

Endpoint: Efficacy - FEV1 mean difference from baseline after use of herbal medicine for 12 weeks
Number of Exacerbations
Reduction in use or dosage of Inhaled Glucocorticosteroids

Safety: Incidence and type of adverse events during study period
Blood levels of flavanoid compounds on the active arm in Phase B.

Statistical analysis: The analysis will be based on data from all patients who were randomised and from whom meaningful data were collected. The primary analysis will be based on the FEV1 measured at baseline and at end of treatment A after week 12 and again at the end of treatment B after week 24. The sample size of 40 randomised patients was chosen to achieve a power of 80% for concluding efficacy, assuming a mean difference of 255 ml was achieved.



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LIST OF ABBREVIATIONS AND DEFINITIONS

The following abbreviations and specialist terms are used in this study protocol:

Abbreviation	Explanation
AE	Adverse Event
ATS	American Thoracic Society
a.n.	as needed
AUC	Area Under Concentration Curve
b.i.d	<i>bis in die</i> = twice daily
CAM	Complementary and Alternative Medicine
CI	Confidence Interval
CRF	Case Report Form
FEV1	Forced Expiratory Volume in first second
GCP	Good Clinical Practice
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IGCS	Inhaled Glucocorticosteroids
PEF	Peak Expiratory Flow
MDI	Metered Dose Inhaler
ml	milliliter
n	Sample size
SD	Standard Deviation
SAE	Serious Adverse Event
UWC	University of the Western Cape

Definitions

Herbal Medicines: Mainly whole, fragmented or cut plants, part of plants in an unprocessed state, usually in dried form, but sometimes fresh. Herbal drugs are precisely defined by the botanical scientific name according to the binomical system (genus, species, variety).

African traditional medicine: The total body of knowledge and techniques for the preparation and use of substances, measures and practices that are based on the socio-cultural and religious bedrock of African communities, are founded on personal experience and observations handed down from generation to generation, either verbally or in writing, and are used for the diagnosis, prevention or elimination of imbalances in physical, mental or social well-being.

Traditional healers: Persons recognized by the community in which they live as competent to practice medicine. There is a social consensus conferring a special status (given different names depending on language concerned) on such healers and granting them the power to heal or even to prevent illness.

1 INTRODUCTION

1.1 Background

Asthma is one of the most common chronic diseases in modern society and there is increasing evidence to suggest that its incidence and severity are increasing. There is a high prevalence of usage of complementary medicines for asthma, such as herbal preparations. Physical evidence of the use of herbal remedies for asthma dates back approximately 5000 years. Four out of five classes of drugs currently used to treat asthma (β 2-agonists, anticholinergics, methylxanthines and cromones) have origins in herbal treatments.

However, recent evaluation of the recommendations of leading Complementary and Alternative Medicine books for specific medical conditions, demonstrated the dominance of opinion over evidence. Although the time has come to replace opinion by evidence, randomised clinical trials of CAM are more difficult and methodologically more challenging than pharmaceutical clinical trials.

1.2 Rationale for this study

Literature searches found seventeen randomised clinical trials on herbal medicines for asthma. Nine of the seventeen trials reported a clinically relevant improvement in lung function and /or symptom scores.

Historically, *Artemisia afra* has been used to treat respiratory illnesses, including asthma, coughs, bronchitis and influenza. The active ingredients in *Artemisia afra* include flavanoid compounds. Flavanoid-rich extract of leaves of the *Ginkgo biloba* tree has been studied in a clinical trial and is recommended as a treatment for allergic inflammation and asthma.

Considering the popularity of herbal medicine amongst asthma patients, there is an urgent need for stringently designed randomised clinical trials for herbal preparations in the treatment of asthma. This study will therefore be done to determine if there is any evidence for the clinical efficacy of the herbal plant, *Artemisia afra*, for the treatment of asthma symptoms.

The study has been designed to investigate six months efficacy and safety of *Artemisia afra* - the first twelve weeks in the form of a tea/broth and the latter three 12 weeks in tablet form. The aim of this study is to determine whether the FEV1 and symptom score improve when compared to placebo.

Details of the herbal plant *Artemisia afra*:

Genus: *Artemisia*

Species: *afra*

Other vernacular names: Wilde als; Umhloniyane; Umhloniyane omncane.

Description: Grey-green shrub with aromatic leaves and small, yellow-green ball-shaped flowers
Height 1-2 meters

Distribution: Western Cape, KwaZulu Natal, Swaziland, Lesotho and Transkei in high altitude areas

2 STUDY OBJECTIVES

The primary objective of the study is to examine the bronchodilatory effect of *Artemisia afra* by performing lung function tests and assessing the difference (increase) in FEV1 after treatment of 12 weeks.

The secondary objective of this study is to assess efficacy by assessment of change in day-time and night-time asthma symptoms and nocturnal awakenings due to asthma symptoms. Another objective is to examine whether subjects could change (lower) their dosage of IGCS. Six months' safety and tolerability will be recorded by assessment of incidence and type of Averse events. Blood levels to determine absorption of flavanoid compounds will be done as a safety measurement on a subgroup of subjects on the active treatment arms.

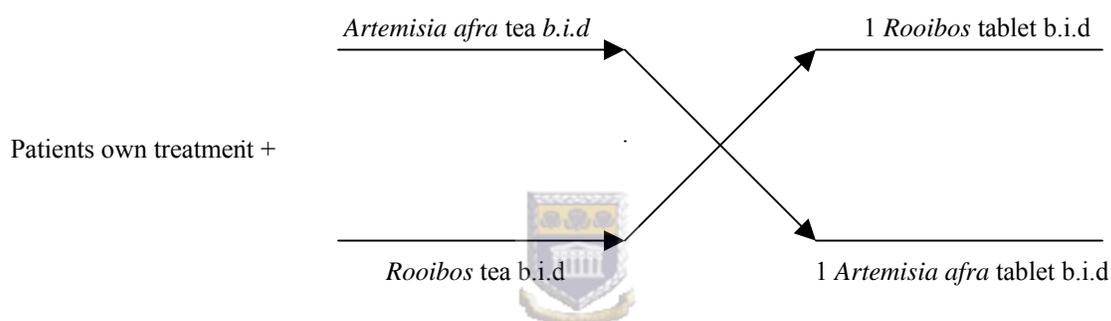


3 STUDY PLAND AND PROCEDURES

3.1 Study design

This is a six months, randomised , single blind cross-over study to examine the bronchodilatory effect of *Artemisia afra*. Subjects must have asthma and be well controlled on maintenance treatment with inhaled corticosteroids and/or rescue medication as needed. Subjects complying with the inclusion and exclusion criteria will be randomised to receive one of the two treatments in the first phase (Phase A). These consist of either the dried plant material of *Artemisia afra* or dried plant material of the placebo Rooibos taken twice daily as a tea for 12 weeks. After the first phase the subjects will cross-over to the above mentioned plants in tablet form for another 12 weeks taken twice daily (Phase B). The subjects will come for 8 visits during the study. All visits will be four weeks (± 3 days) apart and scheduled within ninety minutes from the time of visit 1. Lung function tests will be done at Visit 1, 4 and 7. Blood samples will be taken at Visit 4 and 7 on the active treatment arm in Phase B.

3.1.1 Flowchart



3.1.2 Scheduled clinic visits

Visit number	Type of visit	Number of days between visits
Visit 0	Information visit (if applicable)	
Visit 1	Randomisation visit	30 days before Visit 2
Visit 2	After 1 month's treatment	30 \pm 3 days after Visit 1
Visit 3	After 2 month's treatment	60 \pm 3 days after Visit 1
Visit 4	After 3 month's treatment	91 \pm 3 days after Visit 1
Visit 5	After 4 month's treatment	121 \pm 3 days after Visit 1
Visit 6	After 5 month's treatment	151 \pm 3 days after Visit 1
Visit 7	After 6 month's treatment	181 \pm 3 days after Visit 1

3.1.3 Visits and assessments

Phase A

Week	1	4	8	12
Visit	1	2	3	4
Informed consent	x			
Medical/ asthma/ smoking history	x			
Inclusion/Exclusion criteria	x			
Physical examination, pulse and blood pressure	x			x
Pregnancy test	x			x
Height and weight	x			x
Allocation of patient number	x			
FEV1	x			x
Training with PEF meter	x			
Current and concomitant medication	x	x	x	x
Adverse events	x	x	x	x
Study medication - Dispense/Return	D	R/D	R/D	R/D
Diary – Issue/Return	I	R/I	R/I	R/I
Overall Treatment Evaluation		x		x

* Females of childbearing age

Phase B

Week	16	20	24
Visit	5	6	7
Blood sample (active group only)	x		x
Physical examination, pulse and blood pressure			x
Pregnancy test			x
Height and weight			x
FEV1			x
Current and concomitant medication	x	x	x
Adverse events	x	x	x
Study medication - Dispense/Return	R/D	R/D	R
Diary – Issue/Return	R/I	R/I	R
Overall Treatment Evaluation			x

* Females of childbearing age

3.2 Selection of study population

The study population will be patients with mild to moderate asthma on stable treatment. The investigator should complete a subject screening log to document subjects considered for enrolment, but never enrolled to establish that the subject population is selected without bias.

3.2.1 Inclusion criteria

To be enrolled, the following criteria have to be fulfilled at Visit 1:

1. Outpatients of either sex between 18 and 60 years.
2. Asthma diagnosed according to the ATS definition for at least 6 months prior to Visit 1.
3. Fixed daily use of any brand of IGCS for ≥ 30 days prior to Visit 1.
4. FEV1 ≥ 80 % of the predicted normal.
5. Subjects able to perform acceptable lung function test.
6. Ability to use a peak flow meter correctly.
7. No significant concomitant disease.
8. Signed informed consent. Consent must be obtained before any study-related procedures are conducted.

3.2.2 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Asthma exacerbation within 4 weeks prior to Visit 1, as judged by the investigator.
2. A smoking history of ≥ 10 pack years.
3. Respiratory infection affecting the asthma within 1 month prior to Visit 1.
4. Other pulmonary disease.
5. Pregnancy or Breastfeeding
6. Females of childbearing age potential not using medically accepted contraceptive measures, as judged by the investigator.
7. Subjects who are scheduled to undergo hospitalisation due to surgery during the study.
8. Conditions associated with poor compliance, including alcohol or drug abuse.
9. Participation in a clinical study of any investigational product 1 month prior to visit 1 or during the study.
10. Subjects that would not normally use traditional herbal medicines.

3.2.3 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time, at the discretion of the investigator. Specific reasons for discontinuing a subject from the study are:

1. Withdrawal of informed consent.
2. Development of exclusion criteria, pregnancy or other safety reasons during the study.
3. Protocol non-compliance.
4. Oral corticosteroids treatment due to worsening of asthma for longer than 10 days.
5. Incorrect enrolment or randomisation of the subject.

For subjects withdrawn from the study, the same measurements and assessments should be performed as done at Visit 7. Adverse events should be followed up and diaries, study medication and peak flow meters should be returned by the subjects.

3.3 Investigational Products and Treatments

3.3.1 Treatment period A:

At Visit 1, eligible subjects will receive the study drug in a dried plant form, either the test product *Artemisia afra* or the placebo product. The subjects will brew 2 teaspoons of study medication in 200 ml boiled water and take the tea every morning upon rising and every night before going to bed for 12 weeks. If the subject need more as needed medication than normally in one single day, contact must be made with the investigator for reassessment of the subject's condition.

3.3.2 Treatment period B:

At Visit 4, the subjects will cross-over on their treatment arms and receive the investigational product in tablet form. Subjects will then take one tablet twice daily - every morning and every night as before.

3.3.3 Randomisation

At Visit 1, subjects who are screened for the study will receive an enrolment code: E – code = E + a consecutive number of 3 digits. Subjects who fulfill all inclusion criteria and meet none of the exclusion criteria will be allocated a subject number: S – code = S + a 2 digit number. The order of receiving the test and placebo product will be in accordance with the code of randomisation.

3.3.4 Identity of study drugs

The study drug will be packaged in brown paper bags and marked with the following label:

Study code: UWC 001	Visit no:	
Investigator: Dr	Subject no:	
Investigational product: <i>Artemisia afra</i> or placebo		
Dosage form: 2 teaspoons twice daily		
Store below 30°C		
For clinical study use only		

3.3.5 Storage and Accountability

All study drugs must be kept in a secure place under adequate storage conditions – protected from moisture and light. Records of dispensing and returns will be maintained by the centre. All unused study medication for the treatment period, must be returned by the patient to the trial clinic.

3.4.1 Allowed medication

- i) Inhaled corticosteroids at a stable dose as at Visit 1.
- ii) Other medication (e.g. nasal steroids, antihistamines) at a stable dose will be allowed throughout the study.
- iii) Oral corticosteroids (30 mg per day) for a maximum of 10 days for worsening of asthma.
- iv) The administration of all concomitant medication must be recorded in the appropriate sections of the Case Report Form.

3.4.2 Prohibited medication

- i) Asthma treatment other than the investigational product and the regime used at Visit 1.
- ii) β 2-agonists should be withdrawn for 6 hours before lung function tests. The visit will be rescheduled if the patient do not comply with the withdrawal criteria.

3.4.3 Compliance

The patient will record the use of study medication in a diary on a daily basis and the adherence to the prescribed treatment will be checked at every clinic visit.

4 STUDY MEASUREMENTS AND ENDPOINTS

4.1 Primary efficacy

The mean difference in FEV1 from baseline after 12 week treatment period.

4.2 Secondary efficacy variables

- i) Area Under Response Curve and maximum FEV1 response.
- ii) Asthma exacerbations – see paragraph 4.7
- iii) Reduction in dosage of glucocorticosteroids

4.3 Safety measurements

- i) Daily diary recordings: symptom scores, use of rescue medication and nocturnal awakenings
- ii) Blood levels of flavanoids on a sub-group of subjects on the active treatment arm in Phase B.
- iii) Physical examination
- iv) Adverse Events – see paragraph 4.8

4.4 Screening and demographic measurements

Demographic information (date of birth, sex, race and smoking history), vital signs (pulse, blood pressure, weight (kg) height (cm)) will be recorded at Visit 1. All past and current asthma, medical and surgical history *relevant* for the study will be documented, this includes the asthma history. Asthma should be diagnosed according to the American Thoracic Society (ATS) definition. A physical examination including assessment of general appearance, cardiovascular, lungs, mouth, throat and abdomen will be performed at Visit 1. The examination will be made in accordance with the normal clinical routines at the participating clinics. Fertile females must have a negative pregnancy test. FEV1 will be assessed by spirometry (see paragraph 4.5) to confirm eligibility. The data are to be recorded and collected via Case Report Forms.

4.5 Spirometry

Spirometry should be performed according to the ATS recommendations. Calibrations and services should be performed in accordance with the manufacturer's specification, but calibrations must be conducted on each day it will be used for test purposes. All calibration reports should be signed, dated and filed.

The patient will be recommended not to smoke 1 hour or exercise 2 hours prior to the spirometry measurements. The patient should rest for at least 15 minutes prior to the test. A nose-clip must be used throughout all measurements, but if it not used, it must be case for all measurements. Subjects should sit in an upright position. A mouthpiece should be used and the patient must keep the mouthpiece tightly gripped between lips and teeth, making sure that the tongue is flat to avoid obstruction of the airflow. Leaning forward as the expiration proceeds towards residual volume is undesirable. The same spirometer must be used and preferably the same person must be assisting at the measurements. The subject will perform tidal breathing for a few seconds then inhale as deep as possible and exhale completely. At least three technically satisfactory maneuvers should be performed. A maximum of six maneuvers should be performed until the reproducibility criteria are met. Subjects should be encouraged throughout the procedure. The largest FEV1 is reported and must not exceed the second largest one by more than 5%.

Lung function tests will take place within 90 minutes from Visit 1. Copies of all printouts must be signed and dated and kept in the Case Report Form for source data verification. The printouts must be marked with the patient number, date and time of measurement, visit number and patient initials. Predicted values will be calculated according to the formula of the European Community for Coal and Steel (ECCS). Predicted normal values per gender and age are calculated by the formulas described below:

$$\text{Women FEV1} = 3.95 \times H - 0.025 \times A - 2.60$$

$$\text{Men FEV1} = 4.30 \times H - 0.029 \times A - 2.49$$

H: Standing height in meters
A: age (year)

An ethnic group correction of predicted FEV1 for blacks will be performed by multiplying predicted values by 0.9.

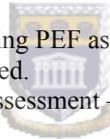
4.6 Measurements recorded daily in a diary

A diary will be filled in at home during the entire study in the morning upon awakening and at night before going to bed. The following variables will be recorded:

- i) morning and evening PEF
- ii) asthma symptom scores
- iii) nocturnal awakenings due to asthma symptoms
- iv) inhalations of rescue medication during the day* and night*
- v) intake of study medication

*Day is defined as the period between the morning PEF assessment - upon rising in the morning - and the evening PEF assessment - just before going to bed.

*Night is the period between the evening PEF assessment – just before going to bed – and the morning PEF – upon rising in the morning.



4.6.1 Morning and evening peak expiratory flow

PEF will be measured using a Mini Wright peak flow meter before intake of any medication directly after awakening in the morning and at bedtime at night. The measurements should be performed in a standing position and at the same time every day. The highest of three efforts will be recorded in the diary. At Visit 1 the subjects will be trained on how to use the peak flow meter in a correct manner and the technique will be monitored throughout the study.

4.6.2 Asthma symptoms

Asthma symptoms will be recorded each morning and evening according to the scores system below:

- 0 = no asthma symptoms
- 1 = you are aware of your asthma symptoms, but can easily tolerate the symptoms
- 2 = your asthma is causing you enough discomfort to cause problems with normal activities or sleep
- 3 = you are unable to do your normal activities (or to sleep) because of your asthma

4.6.3 Nocturnal awakenings

The subjects will in the morning record whether or not they woke up during the night due to their asthma (yes/no).

4.6.4 Intake of rescue medication

The number of inhalations of the rescue/as needed medication will be recorded in the morning and evening. The rescue medication should be used only when the subjects experience asthma symptoms and not more than ten inhalations per day may be taken. If the subjects need more rescue medication in a single day, contact must be made with the investigator for reassessment of the subjects condition.

4.6.5 Time of intake of study medication

The subjects will record the time (morning and evening) that the study medication has been taken. The recordings are a measurement of compliance.

4.7 Asthma exacerbation

Asthma exacerbations occur when the subjects experience a worsening in their asthma symptoms. An asthma exacerbation must contain one of the following events-
Use of oral glucocorticosteroids due to asthma, as judged by the investigator
Hospitalisation/emergency room treatment due to asthma.

4.8 Adverse events

An adverse event is the development of an undesirable medical condition - e.g. symptoms or abnormal results of an investigation - or the deterioration of a pre-existing medical condition. AE's will be collected by means of a standard question: "Have you had any health problems since the previous visit?" AE's will be recorded at every visit. Spontaneously reported AE's and/or observed AE's and the subject's response to this question will be recorded on the AE form with information about seriousness, action taken, date of onset and recovery, maximum intensity and outcome. The subjects will be asked to assess the intensity of the reported Adverse Event according to the following scale:

Mild = awareness of sign or symptom, but easily tolerated
Moderate = discomfort sufficient to cause interference with normal activities
Severe = incapacitating, with inability to perform normal activities.

All changes in the subject's ordinary medication e.g. dose change or new added medication, must be reported in the Medication Log. Reasons for changes in medication which reflect an AE must be recorded on the AE form.

Pregnancy in itself is not regarded as an adverse event, unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication.

A Serious Adverse Event is an adverse event occurring during any phase of the study and at any dose of the investigational product or placebo, that fulfils one or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-subject hospitalisation;
- Results in persistent or significant disability or incapacity.

The causality of Serious Adverse Events (i.e. the relationship to study treatment) will be assessed by the investigators, who in completing the relevant Case Report Form must answer 'yes' or 'no' to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the study medication?" The following factors should be considered when deciding if there is a "reasonable possibility" that an Adverse Event may have been caused by the investigational product.

- Time course of events and exposure to suspect drug – did the AE occur in a reasonable temporal relationship to the administration of suspect drug?
- Dechallenge experience – did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- Rechallenge experience - did the AE reoccur if the suspected drug was reintroduced after having stopped?
- Laboratory tests – has a specific laboratory investigation confirm the relationship?
- No alternative cause - the AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs or environmental factors.

There would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course, but any dechallenge is negative or there is another more likely cause of the AE.

4.8 Overall Treatment Evaluation

All patients will answer a global question about the overall effect of the treatment according to whether he/she has improved or deteriorated with respect to activity limitations/symptoms/emotions related to their asthma. The investigator or delegate will put the question to the patient at the clinic on Visits 3 and 5 i.e. after 12 week treatment periods. The response options are presented as ranging from “ineffective, slightly effective, effective and very effective”.

5 STATISTICAL METHODS

5.1 Determination of sample size

A sample size of 40 patients was chosen to achieve a power of 80% for concluding efficacy, assuming a mean FEV1 difference of 255 ml was achieved.

5.2 Statistical analysis

An intention to treat (ITT) approach will followed, i.e. statistical analysis of efficacy will be based on data from all patients who were randomised and from whom meaningful data were collected. Data will be displayed graphically for visual inspection. The primary variable is based on absolute change in FEV1 from baseline to end of treatment. Efficacy will be obtained at the minimum important clinical difference of 255 ml, therefore

H : $U2 - U1 \geq 255$ ml (effective)

Ha : $U2 - U1 < 255$ ml (not effective)

U2 = after treatment

U1 = at baseline

The Area Under Curve measurements will be calculated with the absolute change from baseline FEV1 to end of treatment data.

Each diary variable will be compared between the two treatment groups by calculating the average values for available data during the whole treatment period and analysed using an analysis of variance model.

5.3 Changes to the Clinical Study Protocol

The Medicines Control Council and the Local Ethics Committees will be notified of any amendments to the Clinical Study Protocol and no changes will be effected without approval from the Regulatory Authorities.

6 ETHICS

6.1 Ethics review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by the Ethics Committees and MCC. The Principle Investigator must also provide the regulatory bodies with any reports of Serious Adverse Events from the study site.

6.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles in the Declaration of Helsinki (see Appendix 10.1), Good Clinical Practice and applicable regulatory requirements.

6.3 Subject information and consent

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any study specific procedure. The investigator must store the original, signed Written Informed Consent Form and a copy must be given to the subject.

6.4 Subject data protection

The Written Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality. Subjects in this database will be identified by initials or enrolment code/subject number only. Authorised representative of a regulatory authority may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history for data verification purposes.

The Investigator must keep a Subject Identification List of all patients that have signed the informed consent, including subject number, full name and last known address.

7 DATA QUALITY ASSURANCE

During the study an independent monitor will be visit the investigational site to confirm that the facilities remain acceptable, that the investigational team is adhering to the protocol and that data are being accurately recorded in the CRFs. Source data verification (a comparison of the data in the CRF with the subject's hospital/practice and other source documents) will also be performed.

Authorised representatives of the Regulatory authority may visit the centre to perform inspections, including source data verification.

Clean File for the final database will be declared when all data have been entered and a quality check on a sample of the data has been performed. The database will be locked after Clean File has been declared and data extracted for statistical analysis.

Study committee meetings will be held as needed prior to or during the study. The medical, nursing and other staff involved in the study will receive proper education/information on how to conduct the study according to the protocol.

8 STUDY TIME TABLE AND TERMINATION

First patient in Phase A	January 2004
Last patient out PhaseA	June 2004
First patient in Phase B	April 2004
Last patient out Phase B	September 2004
Clean File	October 2004
Study Report	December 2004



9 REFERENCES

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- 18) European Harmonisation for Herbal Medicinal Products. www.edqm.org

APPENDIX 10.1

DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. 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."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged

must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate 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.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical 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 consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial

results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared

in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

FOOTNOTE:

NOTE OF CLARIFICATION ON PARAGRAPH 29 of the WMA DECLARATION OF HELSINKI

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

06.10.2002 09h00

Clinical Study Protocol
Drug Substance: *Artemisia afra*

APPENDIX 10.2

PATIENT INFORMATION LEAFLET AND INFORMED CONSENT

Centre _____
Subject initials _____
Enrolment No _____

TRIAL NUMBER: UWC001

TRIAL TITLE: SMart - a Single blind, randomised, placebo controlled asthma trial in patients with Mild to Moderate asthma, to investigate efficacy of the herbal plant *Artemisia afra*.

INTRODUCTION

You are invited to volunteer for a research study focusing on the development of traditional herbal medicines. This information leaflet is to help you decide if you would like to participate. Before you agree to take part in this study, you should full understand what is involved. If you have any questions which are not full explained in this leaflet, do not hesitate to ask the investigator. You should not agree to take part unless you are completely happy about the procedures involved. In the best interest of your health it is strongly recommended that you discuss with or inform your personal doctor of your possible participation in this study, wherever possible.

WHAT WILL HAPPEN DURING THE TRIAL?

You have been diagnosed as suffering from asthma and the investigator would like you to consider taking part in the research of a herbal plant, called *Artemisia afra* (also known as Wildeals). You will receive the study medication in a dried leave form and will be asked to make a tea/broth which you will take every morning and every night for 12 weeks. Thereafter you will take the plant in a tablet form, also every morning and every night for 12 weeks. During the study you will receive either the active agent or a placebo. A placebo is an inactive substance. Lung function tests will be performed at Visit 1, 4 and 7. You will receive a Peak Flow Meter (PEF meter) to measure your lung function every morning and evening and those values should be noted in the diary that will be supplied. Throughout the study you will be asked to fill in the diary with information about total number of rescue inhalations, asthma symptoms and number of times you wake up during the night, due to your asthma. The diary should be filled in each morning and evening and at all clinic visits you

should bring your diary and medication not used. At Visit 2-7 we will ask if you have experienced any adverse events between the visits. You will also be asked to answer a question about the effectiveness of the study medication. If you are a woman of childbearing potential you must use adequate contraception and you should not be pregnant or breastfeeding. You should not be taking part in the study if you are actively planning a pregnancy during the course of the study.

It is important that you let the investigator know of any medicines (both prescriptions or over-the-counter medicines), alcohol or other substances that you are currently taking.

WHAT IS THE DURATION OF THIS TRIAL?

If you decide to take part you will be one of approximately 40 patients. The study will last for up to 24 weeks and each visit will take about one hour. You will be asked to visit the investigator 7 times as per the following schedule:

Visit 1 - (week 1) Randomisation visit

Visit 2 - (week 4)

Visit 3 - (week 8)

Visit 4 - (week 12)

Visit 5 - (week 16)

Visit 6 - (week 20)

Visit 7 - (week 24) Final visit



WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

The information we get from this study will contribute to improve and increase the knowledge of herbal treatment for asthma.

HAS THE TRIAL RECEIVED ETHICAL APPROVAL?

This clinical Protocol was submitted to a local Ethics Committee - Pharma Ethics and the Medicines Control Council and written approval has been granted by the committees on ___/___/2003 and ___/___/___ respectively. The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2000), which deals with the recommendations guiding doctors in biomedical research involving human subjects, a copy of which may be obtained from the investigator should you wish to review it.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS TRIAL?

Your participation in this trial is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. Your withdrawal will not affect your access to other medical care. The investigator retains the right to withdraw you from the study if it is considered to be in your best interest. If it is detected that you did not give an accurate history or did not follow the guidelines of the trial and the regulations of the trial facility, you may be withdrawn from the trial at any time.

APPENDIX 10.3

DIARY FOR TREATMENT PERIOD

Study No: UWC 001

Pat No _____

Morning recordings

Date							
PEF, highest out of 3 measurements							
How many inhalations of rescue Medication did you take during the night?							
Night time asthma score							
Did you wake up during the night due to asthma symptoms?							
Time you took your study medication							

Night = between your evening PEF and your morning PEF upon rising.

Evening recordings

PEF, highest out of 3 measurements							
How many inhalations of rescue Medication did you take during the day?							
Day time asthma score							
Time you took your study medication							

Day = between your morning PEF and your evening PEF, just before going to bed

Asthma symptom score

0 = No asthma symptoms

1 = You are aware of your asthma symptoms but can easily tolerate the symptoms

2 = Your asthma is causing you enough discomfort to cause problems with normal activities

3 = You are unable to do your normal activities (or sleep) because of your asthma

APPENDIX 2

Documentation for MCC – Clinical trial application





University of the Western Cape

School of Pharmacy, Discipline Pharmacology

Private Bag X17, Bellville, 7535 South Africa

School of pharmacy: Tel: + 27 21 959-2190; Fax: +27 21 959 3407

Direct tel. line: +27 21 959 2192; Direct fax: +27 21 9591324; cell: 0822023315.

ref: 03JSL050

23 September 2003

The Registrar
Medicines Control Council
Department of Health
11 Floor Room 1133
Hallmark Building
Proes Street
PRETORIA 0001

Dear Ms Matsotso

Re: APPLICATION TO CONDUCT A CLINICAL TRIAL

Please find enclosed our application to conduct a clinical trial entitled: **A pilot study on mild to moderate asthmatic subjects to test the bronchodilator effect of the herbal plant *Artemisia afra*.**

There are however several, perhaps unusual, aspects which I specifically want to draw to your attention.

Firstly, this submission forms part of the research programme of a student (Ms Anthea van Wyk) who is doing M Pharm degree studies, under my direction at UWC. The topic of her thesis is entitled: Guidelines for Clinical Trials of Traditional plant medicines – comparison with guidelines for allopathic medicine trails and application to the study of anti-asthma plant medicines. Thus the preparation and submission of this application as well as the eventual conduct of the trial (when approved) forms part of that research project. In addition this study also forms part of an overall research programme focused on the preparation and evaluation of plant medicines products. In fact, the study straddles 2 current NRF funded projects, these being:

1. Asthma Plant Medicines Project (NRF6233)- (Descriptive title: The effects, active principles and dosage forms of traditional plant medicines used in asthma in South Africa).
2. Biopharmaceutics of Herbal Products (NRF703339) (Descriptive title: Investigation of the pharmacokinetics of flavonoids and the development of tablet dosage forms of flavonoid-containing plant material).

An application for specific funding of this project may also be submitted to the MRC.

Secondly, this is a clinical trial on a traditional remedy for which, as far as I know, well-established guidelines for applications and conduct of clinical trials on such medicines are not widely available. Thus, we have in this present submission largely followed the current guidelines set for trials with regular medicines. In addition, we have however also looked at some of the other existing guidelines pertaining to the herbal medicines (e.g. the WHO Guidelines for Clinical Trials on Herbal Medicine and the European Agency for the Evaluation of Medicinal Products Guidance on Specifications for herbal drugs, herbal preparations and herbal medicinal products (CPMP/QWP/2820/00), etc), paying special attention to issues such as the requirements w.r.t the investigational product, selection of the subjects, and safety measures. For instance, in this study we will evaluate the product in its traditionally used tea

UWC: A Place of Quality, A Place to Grow

Prof James A Syce, School of Pharmacy, Discipline of Pharmacology, UWC

form, as well as in tablet form. These products will be prepared, pharmaceutically evaluated and certified, prior to use, in the Pharmaceutics Department of the School of Pharmacy. To cover issues w.r.t subject selection the protocol has been submitted to an independent ethics committee. However, to fulfill one of the objectives of Ms van Wyk's Master degree studies, the study will also be submitted to at least one other ethics committee, e.g. UWC Senate Research committee and/or University of Stellenbosch's Pharmaceutical Trials Committee.

Thirdly, another motivation for the submission is the development of our site and expertise to develop and fully evaluate such herbal products in future clinical trials. Thus the evaluation of subjects will occur at the UWC Campus Health Centre while the preparation, pharmaceutical evaluation and storage of the investigational products will occur in the Pharmaceutics Division of the School of Pharmacy and the blood level assays in the Pharmacology Division of the School of Pharmacy, UWC (with initial assistance from PROMEC lab at MRC). The following facilities will be available: lockable drug cabinet with limited access; separate cupboard for case report forms; access to consultation rooms & a spirometer; and a separate room to monitor the data. This is the first submission from this site, but others (under the auspices of the South African Herbal Science and Medicine Institute at UWC) are expected to follow, hence our desired to develop the site as speedily as possible.

We will be very appreciative if the committee will consider and keep the above-mentioned aspects in mind and will welcome any feedback on them.

I trust that our documentation is complete, but if anything is still lacking please let me know.

Yours faithfully



Prof J A Syce
Deputy Dean Faculty of Natural Science and
Coordinator: School of Pharmacy Postgraduate Studies Programme

SOUTH AFRICA : CLINICAL TRIAL APPLICATION

SECTION 1 – CHECK-LIST OF REQUIRED DOCUMENTATION

To be completed by Applicants for all Clinical Trials

COVER SHEET

Study Title: A pilot study on Mild to Moderate Asthmatic subjects to test the bronchodilatory effect of the herbal plant *Artemisia afra*.

Protocol No: UWC 001

Version No: 01

Date of Protocol: September 2003

Study Drug: *Artemisia afra*

MCC Ref number (if applicable): NA

MCC Ref number(s) of comparator drug(s) (if applicable): NA

MCC Ref number(s) of concomitant drug(s) (if applicable): NA

Date(s) MCC approval of previous protocol(s): Not applicable

Sponsor: School of Pharmacy, University of the Western Cape

Applicant: Prof James Syce



Contact Person: Prof James Syce

Address: School of Pharmacy
University of the Western Cape
Private Bag X17, Bellville, 7535

Telephone Number: 021 959 2192

Fax Number: 021 959 1324

Cell Number: 082 202 3315

e-mail address: jsyce@uwc.ac.za

To be completed by MCC

Date original application received:

Tracking No:

Proposed Clinical Trials Committee Meeting Date if applicable:

Signature:

Date:

ACKNOWLEDGEMENT OF RECEIPT OF CTA (Contact details to be completed by the applicant). Whole cover sheet to be faxed to applicant once details in block above are completed.

Contact Details: Name :

Fax No.:

Receipt of new application is hereby acknowledged.

Date:

Signature (of MCC recipient):

Name:

Declaration by applicant:

We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

We, the undersigned, agree to ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and South African legal, ethical and regulatory requirements.



23 September 2003

Applicant (local contact)

Date

National Principal Investigator /
National Co-ordinator /
Other (state designation)

Date

SECTION 2 – ADMINISTRATIVE AND SUPPLEMENTARY DETAILS

Title: A Pilot study on Mild to Moderate Asthmatic subjects to test the bronchodilatory effect of the herbal plant *Artemisia afra*.

Protocol Number/identification: UWC 001

Date of protocol (initial/final): September 2003

Part 1: CONTACT DETAILS (NAME/ADDRESS/TEL/CELL/FAX/E-MAIL)

1.1 Applicant: (as in Section 1)

Prof James Syce

School of Pharmacy

Dept of Pharmacology

University of the Western Cape

Private Bag X17

Bellville 7535

Tel no 021 959 2192

Fax no 021 959 1324

Cell no 082 202 3315

e-mail jsyce@uwc.ac.za

1.2 Sponsor: (as in Section 1) NA

1.3 If no sponsor – person or organisation initiating, managing, and / or funding the clinical trial:

School of Pharmacy

Dept of Pharmacology

University of the Western Cape

Private Bag X17

Bellville 7535

1.4 Local Contact Person for correspondence: Prof James Syce

School of Pharmacy

Dept of Pharmacology

University of the Western Cape

Private Bag X17

Bellville 7535

Tel no 021 959 2192

Fax no 021 959 1324

Cell no 082 202 3315

e-mail jsyce@uwc.ac.za



1.5 National Principal Investigator/Coordinator: (or equivalent person)

Prof P Mugabo

School of Pharmacy

University of the Western Cape

Private Bag X17

Bellville 7535

Tel no: 021 959 3441

Fax no: 021 959 3407

Cell no: 082 202 3589

e-mail: pmugabo@uwc.ac.za

1.6 International Principal Investigator: NA

1.7 Regional Monitor: (as in Section 1)

Laurie Ben-yair

54 Mont Serrat

Balmoral Road

Westbeach 7441

Tel no 021 554 5454

Fax no 021 554 5454

Cell no 083 457 6050

e-mail laurieb@onqsa.co.za



Part 2: DETAILS OF INVESTIGATIONAL PRODUCT(S)

2.1 Name(s) and details of investigational product(s) to be used in trial: [Formulation(s) and strength(s) (e.g. 10 mg/ml–10ml amp.)] Include MCC registration number and date of registration if applicable. Herbal plant -*Artemisia afra*

2.2 Name(s) and details (as above) of comparator product(s) and MCC registration number(s) and date(s) of registration if applicable: [Ensure package inserts or complete pharmacological information been included (Section 1).] NA

2.3 Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required in the protocol, and MCC registration number(s) if applicable: [Ensure package inserts or complete pharmacological information has been included with application (Section 1). Patients will continue with their regular medication for Asthma

2.4 Estimated Quantity of Trial Material (each drug detailed separately) for which exemption will be required: 10 kg of raw plant material to use as tea/broth and 10 kg of raw plant material to use for the preparation of tablets.

2.5 If any of the above drugs are available in South Africa, give an explanation for not using what is available in South Africa: NA

2.6 Details of receiving of drugs from supplier, storage, dispensing, packaging of drugs: The raw plant material will be sourced from the Montaque Botanical Museum and/or White A Chemist in Cape Town. The dried plant material will be packed into teabags and prepared as tablets in the Pharmaceutics Laboratory at the UWC, where it will also be stored until dispensed.

2.7 Date MCC registration applied for – or envisaged date of application for trial medication. Explain if registration is **not** envisaged: Trial for academic reasons only

2.8 Registration status of entity, for the indication to be tested in this trial, in other countries: (i.e. Country: date registered / date applied for / date registration refused / date registration withdrawn by applicant / date registration cancelled by regulatory authority) [Attach as an appendix if necessary.] Not registered

Part 3: DETAILS OF TRIALIST(s) AND SITE(s)

3.1 Details of Investigator(s): [designation, title: (i.e. principal investigators / investigators) Include Name/Address/Tel/Cell/Fax/E-Mail]

Principal Investigator: Prof P Mugabo

School of Pharmacy

University of the Western Cape

Private Bag X17

Bellville 7535

Tel no: 021 959 3441

Fax no: 021 959 3407

Cell no: 082 202 3589

e-mail: pmugabo@uwc.ac.za

Investigator:

Dr M Bagwandeem

Campus Health Centre

University of the Western Cape

Private Bag X17

Bellville 7535

Tel no: 021 959 3576

Fax no: 021 959 2877

Cell no: 083 255 4807

e-mail:mbagwandeem@uwc.ac.

Co-Investigator : Prof James Syce
 School of Pharmacy
 University of the Western Cape
 Private Bag X17
 Bellville 7535
 Tel no: 021 959 2192 Fax no: 021 959 1324
 Cell no: 082 202 3315 e-mail: jsyce@uwc.ac.za

3.2 Current work-load of Investigator(s): (Number of studies currently undertaken by trialist(s) as principal and/or co- or sub-investigator, and the total number of patients represented by these studies. Time-commitments of researcher(s) in relation to clinical trial work *and* non-trial work.)

Recommended format for response:

Investigator (Name and designation):	Dr P Mugabo Principal Investigator		
Total number of current studies (all stages) on specified date	Number 1	Date 23/09/2003	
Total number of patients / participants for which responsible on specified date	Number 15	Date 23/09/2003	
ESTIMATED TIME PER WEEK [168 hours denominator]		Hours/week	%
4 Clinical trials	Clinical work (patient contact)	20	12
	Administrative work	5	3
<u>Organisation</u> (Practice / university / employer)	Clinical work	5	3
	Administrative work	5	3
5 Teaching	Preparation / evaluation	60	36
	Lectures / tutorials	40	24
<u>Writing up</u> work for publication / presentation		5	3
<u>Reading</u> / sourcing information (e.g. internet searches)		8	5
<u>Other</u> (specify)	Animal research activities	20	12

3.3 Details of Site(s) (Name of site, physical address, contact details, contact person, etc.) Single site

Campus Health Centre

University of the Western Cape

Private Bag x17

Bellville 7535

Prof James Syce

Tel no: 021 959 2192

Fax no: 021 959 1324

Cell no: 082 202 3315

e-mail: jsyce@uwc.ac.za

3.4 Capacity of Site(s): (Number of staff, names, qualifications, experience -- including study co-ordinators, site facilities, emergency facilities, other relevant infrastructure)

2 Full time Medical Doctors

3 Full time Nursing sisters trained in Primary Health Care

3 Full time Administrative staff

Co-ordinator: Anthea van Wyk NHDip Medical Technology

See attached CV



Part 4: PARTICIPANTS (SUBJECTS)

4.1 Number of participants in South Africa: 40

4.2 Total worldwide: 40

4.3 Total enrollment in each SA centre: (if competitive enrollment, state minimum and maximum number per site.) 40

4.4 Volunteer base from which South African participants will be drawn: Day hospitals and university campus

4.5 Retrospective data indicating potential of each site to recruit required number of patients within envisaged duration of trial. (SA Guidelines 2000, Item 3.3, p15) [May be attached. Label clearly as 'Section 2 Item 4.5'] There are currently 13 500 students at the UWC and 300-400 patients daily at each local day hospital – at least four will be targeted.

Part 5: OTHER DETAILS

5.1 If the trial is to be conducted in SA and not in the host country of the applicant / sponsor, provide an explanation: NA

5.2 Estimated duration of trial: 6 months

5.3 Name other Regulatory Authorities to which applications to do this trial have been submitted, but approval has not yet been granted. Include date(s) of application: Pharma Ethics applied 22 September 2003

5.4 Name other Regulatory Authorities which have approved this trial, date(s) of approval and number of sites per country: NA

5.5 If applicable, name other Regulatory Authorities or Ethics Committees which have rejected this trial and give reasons for rejection: NA

5.6 If applicable, details of and reasons for this trial having been halted at any stage by other Regulatory Authorities: NA

5.7 Details if this trial is being undertaken in SADC, any other country in Africa, or any country where there is no regulatory control of clinical trials: NA

5.8 Previous studies using this agent which have been approved by MCC: none known

5.9 If any substudies are proposed as part of this protocol, indicate whether or not they will also be done in South Africa. If not, please explain. NA

6 Part 6: ETHICS

6.1 Ethics Committee responsible for each site, date of approval or date of application:

Pharma Ethics – applied 22/09/2003



6.2 Attach copy of response(s) made by, and/or conditions required by ethics committee(s) if available. Ensure that date of EC response is legible. Awaiting

6.3 State which Good Clinical Practice (GCP) guidelines are being followed. (Particular reference to the South African guidelines required): SAGCP and WHO guidelines for Herbal Medicines Trials

6.4 Details of capacity building component of the trial, if any: Campus Health Centre and School of Pharmacy to be developed for future clinical trials as part of South African Herbal Science and Medicines Institute at the UWC.

6.5 Details of the training of investigators, monitors, study co-ordinators in terms of carrying out this trial and in terms of GCP: Attending accredited GCP courses every 2 years

6.6 Detailed safety and monitoring plan for each site: [May be attached. Label as 'Section 2 Item 6.6'] Monitoring by Laurie Ben-yair at regular intervals and patients can be treated for medical emergencies at the site (Campus Health Centre).

6.7 Details of trial insurance certificate: (e.g. title, protocol, dates, policy #, amount)

The UWC currently has insurance cover, but in the event that the study will be approved and conducted, special cover will be obtained from the Insurance Company for the duration of the trial.

6.8 Details of possible conflict of interest of any person(s)/organisation(s) who/which will be involved in the trial: None

6.9 Remuneration to be received in SA Rands: (Investigators) (Trial participants) (Others) Indicate broad breakdown of costs to be covered by this amount – if applicable. [Note: the CTC recommends a minimum compensation of R50.00 per visit for participants travel and incidental expenses.] No remuneration for trial personnel, as it is for academic purpose only. Study subjects will receive R50.00 travel allowance

Reviewer's comments on Section 2:

SECTION 3 – APPLICANT'S REPORT / PRESENTATION

[Please use Black 12 point Arial Font, using MSWord or rich text format (rtf) for electronic version]

1. Title: A pilot study on Mild to Moderate Asthmatic subjects to test the bronchodilatory effect of the herbal plant *Artemisia afra*

CTC Reviewer's comment:

2. Protocol Number/identification: UWC 001

3. Rationale for study summarised: (Why should this trial be done at all?) Include statement about South African contribution, if any, to the development of this protocol.

CTC Reviewer's comment:

4. **Background information (summarised – essential** points that apply to this trial) [1-2 sentences max for each point]:

Disease / problem :Mild to Moderate Asthma

South African context (e.g. local epidemiology)

Properties of Drug / Entity; hypotheses about mechanism of action, etc.

Traditional Healers in South Africa claims that the herbal plant *Artemisia afra* has anti-asthmatic (i.e. Bronchodilatory) properties

Pre-clinical findings: (e.g. laboratory / animal / toxicity / mutagenicity)

Clinical findings (e.g. phases; PK; PD; dose-finding; ADRs, NNT/NNH, other)

Systematic review(s) and/or citations per year-group on a Medline search

CTC Reviewer's comment:

Pre-clinical findings: (e.g. laboratory / animal / toxicity / mutagenicity).

There are limited/no pre-clinical studies that have been done on *Artemisia afra* itself, but we have found in our laboratory that aqueous extracts of the plant was able to relax guinea pig tracheal muscle which had been contracted by histamine, acetylcholine and leukotriene (ref: J A Syce & L Harris. Preliminary characterization of the effect of *Artemisia afra* on guinea pig airway muscle. Poster at Annual Congress of Society for Medicinal Plant Research, Barcelona Spain, Sept 2002 (*Revista de Fitoterapia Vol 2 Suppl 1, A161*). Individual flavonoids such as luteolin has however been shown to have several effects on cell lines eg. anti-mutagenic, antimourigenic, anti-oxidant, 5-lipoxygenase activity.

Clinical findings (e.g. phases; PK; PD; dose-finding; ADRs, NNT/NNH, other)

No information available, this will be a first study. There have also not been any reports on adverse effects with traditional use.

Systematic review(s) and/or citations per year-group on a Medline search
No systematic reviews found.

CTC Reviewer's comment:



5. Objectives of study (clearly listed and justified)

{The primary objective of this study is to test whether *Artemisia afra* does indeed have any anti-asthmatic properties and whether a tablet dosage form would be similarly active as the traditional liquid dosage form. The major measure for the assessment of the anti-asthmatic effects will be improvement in FEV1 (relative to that caused by placebo). A secondary objective will be to ascertain if the flavonoid luteolin is present in the blood after ingestion of *Artemisia* product (and possibly correlates with the plant medicines anti-asthma activity)}.

A 24 week, randomised, single blind, cross-over study to examine efficacy of *Artemisia afra* versus placebo in subjects with stable asthma with or without maintenance treatment. Patients will also do a daily diary regarding a Peak Flow Volume, symptoms score and need for rescue medication .

Asthma is one of the most common chronic diseases in modern society and there is increasing evidence to suggest that its incidence and severity are increasing. There is a high prevalence of usage of complementary medicines for asthma, such as herbal preparations. Physical evidence of the use of herbal remedies for asthma dates back approximately 5000 years. Four out of five classes of drugs currently used to treat asthma (β 2-agonists, anticholinergics, methylxanthines and cromones) have origins in herbal treatments.

However, recent evaluation of the recommendations of leading Complementary and Alternative Medicine books for specific medical conditions, demonstrated the dominance of opinion over evidence. Although the time has come to replace opinion by evidence, randomised clinical trials of Complementary and Alternative Medicines are more difficult and methodologically more challenging than pharmaceutical clinical trials.

Literature searches found seventeen randomised clinical trials on herbal medicines for asthma. Nine of the seventeen trials reported a clinically relevant improvement in lung function and /or symptom scores.

Historically, *Artemisia afra* has been used to treat respiratory illnesses, including asthma, coughs, bronchitis and influenza. The active ingredients in *Artemisia afra* include flavanoid compounds. Flavanoid-rich extract of leaves of the *Ginkgo biloba* tree has been studied in a clinical trial and is recommended as a treatment for allergic inflammation and asthma.

Considering the popularity of herbal medicine amongst asthma patients, there is an urgent need for stringently designed randomised clinical trials for herbal preparations in the treatment of asthma.

This study will therefore be done to determine if there is any evidence for the clinical efficacy of the herbal plant, *Artemisia afra*, for the treatment of asthma symptoms.

The study has been designed to investigate six months efficacy and safety of *Artemisia afra* - the first twelve weeks in the form of a tea/broth and the latter three 12 weeks in tablet form. The aim of this study is to determine whether the FEV1 and symptom score improve when compared to placebo.

CTC Reviewer's comment:

6. Study design (clearly described and each component justified)
[includes phase, use of placebo, dosages, randomisation, blinding, duration, etc.]

This is a six months, randomised, single blind cross-over study to examine the bronchodilatory effect of *Artemisia afra*. Subjects must have asthma and be well controlled on maintenance treatment with inhaled corticosteroids and/or rescue medication as needed. Subjects complying with the inclusion and exclusion criteria will be randomised to receive one of the two treatments in the first phase (Phase A). These consist of either the dried plant material of *Artemisia afra* or dried plant material of the placebo Rooibos taken twice daily as a tea for 12 weeks. After the first phase the subjects will cross-over to the above mentioned plants in tablet form for another 12 weeks taken twice daily (Phase B). The subjects will come for 8 visits during the study. All visits will be four weeks (\pm 3days) apart and scheduled within ninety minutes from the time of visit 1. Lung

function tests will be done at Visit 1, 4 and 7. Blood samples will be taken at Visit 4 and 7 on the active treatment arm in Phase B.

Trial Phase: Therapeutic exploratory/ Phase II

Test Product, Dose, blinding and mode of administration: *Artemisia afra* as obtained from traditional medicines suppliers in South Africa, 2 teaspoons dried leave product brewed in 200 ml boiled water taken twice daily for 12 weeks for Phase A and 1 tablet of *Artemisia afra* twice daily for 12 weeks in Phase B. Patients will be blinded as to which group they are randomised as the study medication will be packed in brown paper bags and be labeled in a similar way. Study medication will be allocated in blocks of 4 to subjects reporting to the centre.

Placebo: 2 teaspoons Rooibos tea (caffeine free) brewed in 200 ml boiled water administered as a tea taken twice daily for 12 weeks in Phase A and 1 tablet Rooibos twice daily for 12 weeks in Phase B. The use of placebo will enable the researcher to compare the therapeutic efficacy of the herbal plant, but patients will continue with their regular asthma medication.

CTC Reviewer's comment:

7. Participants: (number of participants; ability to enroll required number within stated time) 40 As most asthmatic patients experience symptoms during summer and at the change of season, it is most likely that the required number of patients will be randomised from January to April.

CTC Reviewer's comment:

8. Eligibility and enrollment: (Inclusion and exclusion criteria listed and justified)
Diagnosis Mild to Moderate Asthmatic patients diagnosed according to ATS Criteria

1 Inclusion criteria

9. Outpatients of either sex between 18 and 60 years.

10. Asthma diagnosed according to the ATS definition for at least 6 months prior to Visit 1.

11. Fixed daily use of any brand of IGCS for ≥ 30 days prior to Visit 1.

12. FEV1 ≥ 80 % of the predicted normal.

13. Subjects able to perform acceptable lung function test.

14. Ability to use a peak flow meter correctly.

15. No significant concomitant disease.

16. Signed informed consent. Consent must be obtained before any study-related procedures are conducted.

3.3.2 Exclusion criteria

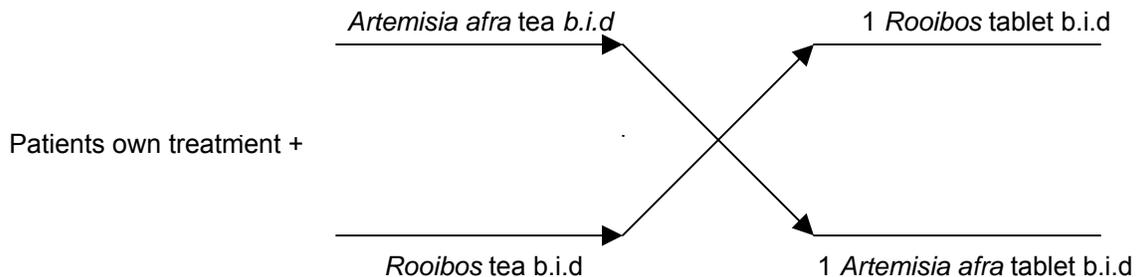
11. Asthma exacerbation within 4 weeks prior to Visit 1, as judged by the investigator.
12. A smoking history of ≥ 10 pack years.
13. Respiratory infection affecting the asthma within 1 month prior to Visit 1.
14. Other pulmonary disease.
15. Pregnancy or Breastfeeding
16. Females of childbearing age potential not using medically accepted contraceptive measures, as judged by the investigator.
17. Subjects who are scheduled to undergo hospitalisation due to surgery during the study.
18. Conditions associated with poor compliance, including alcohol or drug abuse.
19. Participation in a clinical study of any investigational product 1 month prior to visit 1 or during the study.
20. Subjects that would not normally use traditional herbal medicines.

CTC Reviewer's comment:

9. Treatment modalities and regimens, drug accountability [clearly explained and justified for all participant groups/arms e.g. in terms of route of administration, dose, etc. Drug accountability clearly described.]

Artemisia afra as obtained from traditional medicines suppliers in South Africa, 2 teaspoons dried leave product brewed in 200 ml boiled water taken orally twice daily for 12 weeks for Phase A and 1 tablet of *Artemisia afra* twice daily for 12 weeks in Phase B.

Flowchart



Drug accountability:

Patients will receive grams of dried plant product at each visit for 4 weeks. At the next visit the returned study medication will be weighed and compliance calculated.

CTC Reviewer's comment:

10. Outcome measurements/variables (each clearly stated and justified)

Primary efficacy:

The mean difference in FEV1 from baseline after 12 week treatment period.

Secondary efficacy variables:

- iv) Area Under Response Curve and maximum FEV1 response.
- v) Asthma exacerbations
- vi) Reduction in dosage of glucocorticosteroids

Safety measurements:

- v) Daily diary recordings: symptom scores, use of rescue medication and nocturnal awakenings
- vi) Blood levels of flavanoids on a sub-group of subjects on the active treatment arm in Phase B.
- vii) Physical examination
- viii) Adverse Events

CTC Reviewer's comment:

11. Adverse events (prevention, definitions – including causality assignment, recording, reporting, time-lines, action to be taken, all clearly described)

An adverse event is the development of an undesirable medical condition - e.g. symptoms or abnormal results of an investigation - or the deterioration of a pre-existing medical condition. AE's will be collected by means of a standard question: "Have you had any health problems since the previous visit?" AE's will be recorded at every visit. Spontaneously reported AE's and/or observed AE's and the subject's response to this question will be recorded on the AE form with information about seriousness, action taken, date of onset and recovery, maximum intensity and outcome. The subjects will be asked to assess the intensity of the reported Adverse Event according to the following scale:

- Mild = awareness of sign or symptom, but easily tolerated
- Moderate = discomfort sufficient to cause interference with normal activities
- Severe = incapacitating, with inability to perform normal activities.

All changes in the subject's ordinary medication e.g. dose change or new added medication, must be reported in the Medication Log. Reasons for changes in medication which reflect an AE must be recorded on the AE form.

Pregnancy in itself is not regarded as an adverse event, unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication.

A Serious Adverse Event is an adverse event occurring during any phase of the study and at any dose of the investigational product or placebo, that fulfils one or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-subject hospitalisation;
- Results in persistent or significant disability or incapacity.

The causality of Serious Adverse Events (i.e. the relationship to study treatment) will be assessed by the investigators, who in completing the relevant Case Report Form must answer 'yes' or 'no' to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the study medication?" The following factors should be considered when deciding if there is a "reasonable possibility" that an Adverse Event may have been caused by the investigational product.

- Time course of events and exposure to suspect drug – did the AE occur in a reasonable temporal relationship to the administration of suspect drug?
- Dechallenge experience – did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- Rechallenge experience - did the AE reoccur if the suspected drug was reintroduced after having stopped?
- Laboratory tests – has a specific laboratory investigation confirm the relationship?
- No alternative cause - the AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs or environmental factors.

There would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course, but any dechallenge is negative or there is another more likely cause of the AE.

CTC Reviewer's comment:

12. Statistical measures:

Determination of sample size correct, clear and justified (with and/or without stratification)

A sample size of 40 patients was chosen to achieve a power of 80% for concluding efficacy at a significant level of 5%, assuming a mean FEV1 difference of 255 ml was achieved.

Statistical method(s) and analysis of quantitative measures appropriate, clear and justified

Statistical analysis:

An intention to treat (ITT) approach will followed, i.e. statistical analysis of efficacy will be based on data from all patients who were randomised and from whom meaningful data were collected. Data will be displayed graphically for visual inspection. The primary variable is based on absolute change in FEV1 from baseline to end of treatment. Efficacy will be obtained at the minimum important clinical difference of 255 ml, therefore

H : $U2 - U1 \geq 255$ ml (effective)

Ha : $U2 - U1 < 255$ ml (not effective)

U2 = after treatment

U1 = at baseline

The Area Under Curve measurements will be calculated with the absolute change from baseline FEV1 to end of treatment data.

Statistical method(s) and analysis of qualitative measures appropriate, clear and justified

Each diary variable will be compared between the two treatment groups by calculating the average values for available data during the whole treatment period and analysed using an analysis of variance model.

Data processing (how, where, when, who) clearly described and justified. If a SA person will be involved in data processing, please identify that person
Interim analysis envisaged or not (justify) and stopping rules if applicable (explain)

The data will be processed by the University of the Western Cape under supervision of Prof James Syce

CTC Reviewer's comment:

13. Ethical Issues: justification of 'Section 2 part 6' including:

- Explanation of which GCP guidelines are or are not being followed – with particular reference to the South African guidelines
- Comment on choice of investigators (refer to point C of Introduction, page 2 SA Clinical Trials Guidelines 2000)
- Comment on need for, appropriateness of, and relevance of GCP training / updating / for staff involved in this trial
- Comment on capacity building element of trial
- Comment on resources of sites and sponsor
- Comment on monitors and monitoring plan
- Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and regulatory requirements
- Comment on insurance and indemnity measures
- Comment on Patient Information Leaflet and Informed Consent (NB: inclusion of ABPI guidelines; appropriate level of education/English; possible benefits / risks clear; ensuring patient rights; contact names and numbers, as well as MCC details, included)
- Comment on availability and completeness of separate PILs and informed consent forms for any proposed archiving of blood specimens for later research or for genetics research.
- Comment on ethics of the publication policy
- Comment on treatment and/or management of participants and their disease condition(s) after completion of trial
- Comment on ethics committee capacity to monitor site if not a local ethics committee
- Provide an explanation if minimum recommended compensation for participants is not being provided.

CTC Reviewer's comment:

7 14. Other relevant information not included above

E.g. Are references adequate and dates of references current?

Are there discrepancies between protocol and IB or package inserts? Are there specific explanation(s) for these discrepancies?

Are the explanations for not following the SA 'GCP guidelines' acceptable?

Other comments on this trial.

CTC Reviewer's comment:

For office use:

CTC Reviewer's questions and concerns to be considered and/or forwarded to applicant:

CTC Reviewer's recommendation:

APPENDIX 3

Response from MCC on protocol submission



MEDISYNEBEHEERRAAD

Republiek van Suid-Afrika



MEDICINES CONTROL COUNCIL

Republic of South Africa

DIE REGISTRATEUR VAN MEDISYNE
DEPARTEMENT VAN GESONDHEID
PRIVAATSAK X828
PRETORIA
0001

Telephone: (012) 312-0000
Telefoon: (012) 312-0000
Faks: (012) 326-4344
Fax: (012) 326-4344

THE REGISTRAR OF MEDICINES
DEPARTMENT OF HEALTH
PRIVATE BAG X828
PRETORIA
0001

FAX AND MAIL TO

Prof J Syce
School of Pharmacy, Dept of Pharmacology
University of the Western Cape
Private Bag X17
Bellville
7535
Fax: 0219591324

Navrae • Inquiries: N2/19/B/2 (2027)
Verwysing • Reference: 26 November 2003
Datum • Date

MRS NAOMI LESHABANE

Tel: 0123120279
Fax: 0123120389

Dear Prof Syce,

Your application of the attached protocol has the following recommendations from the Clinical Trials Committee (CTC).
Please respond to the attached recommendations within 7 days of receipt ^{05 DECEMBER} ~~(26 November 2003)~~, so as to assist the MCC in the timeous review and approval of your application.

- TWO copies of your response must please be forwarded to the clinical trials unit by mail OR hand delivered.
- Note that even if your trial category has 1 or 2, it still has to be ratified at the coming Medicines Control Council meeting.
- Please note that the study cannot commence until a final approval is obtained after the MCC meeting.

Please ensure that you indicate that it is a *RESPONSE* to the CTC meetings held on the for the Council meeting scheduled for the 28 November 2003

Yours faithfully,

Naomi Leshabane 26/11/03
MRS NAOMI LESHABANE

FOR AND ON BEHALF OF REGISTRAR OF MEDICINES

MCC TRIAL REFERENCE NO: 20031039



MCC REF NO: N2/19/8/2 [2027]
STATUS: 8.1.15
APPLICANT: PROF J SYCE
MEDICINE: ARFTEMISIA AFRA
PROTOCOL: UWC 001
TITLE: A pilot study on mild to moderate asthmatic subjects to test the bronchodilatory effect of the herbal plant Artemisia afra

CTC RECOMMENDATIONS:

1. Study approval category (5)
2. Study not approved until because of the following reasons:
 - 2.1 No safety data has been submitted and how will the pharmacokinetics of the drugs be addressed.
 - 2.2 Patients should be X Rayed to exclude other pathologies in the chest
 - 2.3 **What** is the place of blood tests for exclusion purposes?
 - 2.4 Safety monitoring is not addressed.
 - 2.5 Question 13 has not been answered.
 - 2.6 Insurance is crucial and has not been addressed.
 - 2.7 Copy of Ethics Committee approval is submitted to MCC.
 - 2.8 The CTC recommends a minimum compensation of R150 per visit for time and out of pocket expenses for the trial participants.

MEDISYNEBEHEERRAAD

Republiek van Suid-Afrika



MEDICINES CONTROL COUNCIL

Republic of South Africa

DIE REGISTRATEUR VAN MEDISYNE
DEPARTEMENT VAN GESONDHEID
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THE REGISTRAR OF MEDICINES
DEPARTMENT OF HEALTH
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0001

FAX AND MAIL TO:

Prof J Syce
School of Pharmacy, Dept of Pharmacology
University of the Western Cape
Private Bag X17
Bellville
7535
Fax: 0219591324

Navrae • Inquiries:

Verwysing • Reference: DR RAJEN MISRA
N2/19/8/2 (2027)

Datum * Date 26 January 2004

Tel: 012 312 0000
Fax: 012 312 3106

Dear Prof Syce,

PROTOCOL: UWC 001

TITLE: A PILOT STUDY OF MILD TO MODERATE ASTHMATIC SUBJECTS TO TEST THE BRONCHODIALTORY AFFECT OF THE HERBAL PLANT ARTEMISIA AFRA

RE : APPLICATION HELD OVER TO NEXT CTC MEETING

Your application letter received on the 01 October 2003 regarding the above mentioned protocol refers

This communication serves to notify you that your study was not discussed at the clinical trials committee meeting held on the 16 January 2004 due to unforeseen circumstances. As a result, your study will be held over and discussed at the next Clinical Trials Committee meeting scheduled for the 20-21 February 2004.

We apologize for the inconvenience caused by this delay and promise that your study will receive priority attention at the next clinical trials committee meeting.

Regards,

DR RAJEN MISRA
FOR AND ON BEHALF OF REGISTRAR OF MEDICINES

ETHICS REFERENCE NO: 20031039



APPENDIX 4

Documentation for Stellenbosch Institutional Review Board –
Application for registration of a research project





University of the Western Cape

School of Pharmacy, Discipline Pharmacology

Private Bag X17, Bellville, 7535 South Africa School of pharmacy:

Tel: + 27 21 959-2190; Fax: +27 21 959 3407

Direct tel. line: +27 21 959 2192; Direct fax: +27 21 9591324; cell: 0822023315.

ref: 04JSL011

11 February 2004

Committee for Pharmaceutical Trials

PO Box 19063

Tygerberg 7505

Tel: 021 938 9075

e-mail: pbarn@sun.ac.za

Dear Ms Petro Neethling

PROTOCOL: UWC001
**TITLE: A PILOT STUDY ON MILDE TO MODERATE
ASTHMATIC SUBJECTS TO TEST THE
BRONCHODILATORY EFFECT OF THE HERBAL PLANT
ARTEMISIA AFRA.**

Please find enclosed the application for the above-mention project for consideration by our Ethics committee. This is a project being done as part of our overall research programme on traditional plant medicines. The project is being done in the School of Pharmacy and Student Health Services of UWC and under the auspices of the South African Herbal Science and Medicines institute. The latter is made up of researchers from several departments at UWC. The application is also being submitted to MCC and the Committee for Pharmaceutical Trials of the University of Stellenbosch (who looks at it on behalf of the UWC Senate Research committee), because an additional aim of our research programme is to establish all the guidelines required for such clinical trials. This particular project also forms part of a Masters degree project.

We trust that we have completed all the required forms appropriately. If not please advise what else is required.

Yours faithfully

Prof J A Syce

Deputy Dean Faculty of Natural Science and

Coordinator: School of Pharmacy Postgraduate Studies Programme

STELLENBOSCH UNIVERSITY - TYGERBERG CAMPUS
APPLICATION FOR THE REGISTRATION OF A RESEARCH PROJECT

A. RESEARCHER

Name	Prof James Syce	ID no	511230 5056 010
Department	School of Pharmacy	Phone no	021 959 2192
Present position	Deputy Dean Faculty of Natural Science	E-mail	jsyce@uwc.ac.za

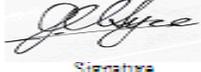
B. PROJECT TITLE – TYPEWRITTEN (MAXIMUM OF 250 CHARACTERS FOR DATABASE PURPOSES)

A Pilot study on Mild to Moderate Asthmatic subjects to test the bronchodilatory effect of the herbal plant *Artemisia afra*

C. INFORMATION FOR THE EVALUATION OF THE ETHICS (COMPLETE EVERY BLOCK WITH A YES OR A NO)

1. Are humans	<input type="checkbox"/> Yes	or animals	<input type="checkbox"/> No	, alive	<input type="checkbox"/> Yes	or dead	<input type="checkbox"/> No	, the subjects of your research?	
2. Will any medicine be tested during the investigation?									<input type="checkbox"/> Yes
2.1 If YES to question 2, is the medicine approved by the Medicines Control Council?									<input type="checkbox"/> No
2.2 If YES to question 2.1, is the medicine registered for the dose which will be used in this specific project?									--
2.3 If YES to question 2.1, is the medicine registered for the indication(s) which will be used in this specific project?									--
2.4 If NO to question 2.1, is the medicine approved by the Medicines Control Council for your use in this specific project?									<input type="checkbox"/> No
2.5 If NO to questions 2.2 and/or 2.3, is the medicine approved by the Medicines Control Council for your use in this specific project?									--
3. Will any radioactive material be administered to the patient during the investigation?									<input type="checkbox"/> No
4. Is any biohazardous material (*) involved in the project?									<input type="checkbox"/> No
5. Have you acquainted yourself with the code of conduct regarding the ethics of research at this institution and do you undertake to fully comply with it at all times?									<input type="checkbox"/> Yes
(*) "Biohazardous material" refers to recombinant DNA molecules, viruses, fungi, parasites, bacteria and all other potentially biohazardous material or products that are dangerous to both the experimental patient and the researcher, and which is patient to strict containment specifications and safety measures.									
X application will be/has been submitted.									

D. SIGNING OF THE APPLICATION

Applicant	Prof James Syce Print name	 Signature	Date	12/02/2004
Supervisor(*)	Print name	Signature	Date	
Departmental Head	Prof James Syce Print name	 Signature	Date	12/02/2004

(*) When a person not medically or dentally qualified intends undertaking research on patients or where access to patient records is required, a medical doctor or a dentist must countersign this application as proof that the research will be executed with his/her consent and under his/her supervision.



CHECKLIST FOR NEW PHARMACEUTICAL TRIAL PROJECTS

PROTOCOL TITLE							
A Pilot study on Mild to Moderate Asthmatic subjects to test the bronchodilatory effect of the herbal plant <i>Artemisia afra</i> .							
PROTOCOL NUMBER	UWC 001	PROTOCOL VERSION	01	PROTOCOL DATE	September 2003		
APPLICANT	Prof James Syce		EVALUATOR				
COMPLETE THE RELEVANT COLUMNS WITH A ✓ .							
CHECKLIST				APPLICANT			EVALUATOR
				YES	NO	N/A	ACCEPTABLE
							YES
A	GENERAL						
1	Has the application form been completed accurately?			✓			
2	Have both the applicant and the relevant head of the department signed the application form?			✓			
3	Have the names of the Sub-Investigator(s) been indicated?			✓			
4	Have the Principal Investigator and Sub-investigator(s)' CV's been attached?			✓			
5	Has the name of the sponsor been indicated?			✓			
6	Has the name of the sponsor's clinical monitor been indicated?			✓			
7	Has the Medicines Control Council's approval of the participation of the applicant been attached?				✓		
8	Has the budget for the trial been attached with full detail?					✓	
9	Has the financial contract/clinical trial agreement been attached?					✓	
10	Does the contract clearly stipulate that the amounts stated are the sole and complete settlements for any compensation involved in the trial?					✓	

11	Does the contract clearly stipulate that all monies and reimbursements due are to be deposited in a registered University fund?			√		
12	Has the correct and valid insurance certificate been attached and does it state that ABPI ¹ guidelines will be complied with?	File note				
13	Has the indemnity form been attached?			√		
B	PROTOCOL					
14	Has the objective of the trial been clearly explained?	√				
15	Has the duration of the trial been indicated?	√				
16	Has the number of patients who will participate in the trial both locally (at this site) and globally (RSA/elsewhere) been indicated?	√				
17	Have the interventions and procedures to be implemented been indicated?	√				
18	Have both the logistical as well as financial arrangements with regard to laboratory and diagnostic imaging procedures been indicated?			√		
19	Are invasive diagnostic procedures, other than the taking of blood and tissue samples, involved?		√			
20	If the answer to the above question is yes, is this essential for the diagnosis and management of the patient?			√		
21	Are invasive diagnostic procedures, other than the taking of blood and tissue samples, involved in the follow-up visits?		√			
22	If the answer to the above question is yes, is this essential for the management of the patient?			√		
23	Is there a written consent form for the persons involved in the invasive investigations?			√		
24	Are there any deviations from the normal standard procedures in the diagnostic and therapeutic management of the patient?		√			
25	Is the quantity of body fluids and tissue samples that will be taken per occasion, and in total, clearly indicated?	√				
26	Has it been indicated whether controls will be used?			√		
27	Has it been indicated whether or not placebo's will be used?	√				
28	Have the anticipated advantages of the medicine(s) been indicated?	√				
29	Is the wording of the anticipated advantages realistic and conveyed in a suitable manner so as not to place unnecessary pressure on the patient to participate in the trial?	√				
30	Have the expected adverse effects of the medicine(s) been indicated?	√				
31	Has remedial treatment in the case of adverse effects been indicated?	√				
32	Has the MCC approved package-insert of the medicine(s) with which the test medicine(s) will be compared been attached?			√		

¹ ABPI: Association of the British Pharmaceutical Industry

33	Will the comparator medicine(s) be administered according to the registered indications, doses and dose intervals as stipulated by the MCC?			√		
34	Have the inclusion criteria been satisfactorily indicated?	√				
35	Have the exclusion criteria been satisfactorily indicated?	√				
36	Have the circumstances under which a patient may be withdrawn from the study been clearly stated?	√				
37	Has it been stated whether or not standard therapy will be discontinued?	√				
38	Has it been indicated where the trial will be conducted (Hospital or faculty building)?	√				
39	Has it been indicated how and where patients will be recruited?	√				
40	Has the proposed advertisement been attached?	√				
41	Has it been indicated whether or not existing facilities and infrastructure are adequate?	√				
42	Has it been indicated which support staff will be involved?	√				
43	If the answer to the above question is yes, is their written assent available?	√				
44	Has it been indicated whether or not follow-up studies are envisaged after the completion of the trial?	√				
45	Has it been indicated whether the trial will be conducted according to the Declaration of Helsinki (version 2000) and ICH guidelines for GCP?	√				
C PATIENT INFORMATION AND INFORMED CONSENT FORM						
46	Has the trial title been correctly stated in the form?	√				
47	Have acceptable lay terms been used to explain the trial?	√				
48	Have the numbers of patients to be used locally as well as globally (RSA/elsewhere) been stated?	√				
49	Has the duration of the trial been indicated?	√				
50	Have lay terms been used to indicate the quantity of body fluids and tissue samples that will be taken on occasion and in total and the intervals thereof clearly been indicated?	√				
51	Has the patient's right to withdraw without any disadvantage to his/her treatment been indicated?	√				
52	Have the anticipated advantages of the trial medication been stated?	√				
53	Is the wording of the anticipated advantages realistic and conveyed in a suitable manner so as not to place unnecessary pressure on the patient to participate in the trial?	√				
54	Have the expected adverse effects of the trial medicine(s) been indicated?	√				

55	Have the adverse effects of the comparator product as indicated in the approved package-insert been clearly reflected in the form?			√		
56	Has the patient been informed that he/she will not be remunerated for his/her participation in the trial, but that he/she may claim for certain expenses incurred by him/her?	√				
57	Has the patient been informed that insurance cover is available should a study-related adverse event occur?	√				
58	Has it been indicated that insurance cover is in accordance with ABPI guidelines?	√				
59	Will the patient be requested to inform his/her general practitioner of his/her participation in the study?	√				
60	Will the patient be requested to inform his/her life insurance company/companies where he/she may have a policy or policies of their participation in the study?		√			
61	Will the patient be informed that all data collected during the study will be kept strictly confidential?	√				
62	Will the patient be informed that results of the study will be made public and may be published without compromising confidentiality?	√				
63	Are the name(s) and telephone number(s) of the investigator(s) who will be on call on a 24-hour basis, and in emergencies, provided?	√				
64	Has it been indicated that the CPT ² of Stellenbosch University has approved the study?	√				
65	Has it been indicated that alternative treatments are available?	√				
66	Are the generic names (as registered in the RSA) of the alternative and rescue medications indicated?			√		
67	Is a form available in all the languages relevant to the target population that will be studied?	√				
68	Do the contents (headings and wording) of the forms correspond in all the versions?			√		
69	Has it been indicated if and how the treatment will be available after the study has been completed?	√				
70	Has it been indicated that the study will be conducted according to the Declaration of Helsinki (version 2000) and to ICH guidelines for GCP?	√				

SIGNED BY:

APPLICANT



DATE

DEPARTMENT HEAD

DATE

EVALUATOR

DATE

**Committee for Pharmaceutical Trials
Protocol synopsis**

² Committee for Pharmaceutical Trials of Stellenbosch University

SECTION 1: DETAILS OF APPLICANT/PRINCIPAL INVESTIGATOR

DETAILS OF PRINCIPAL INVESTIGATOR

NAME AND TITLE : PROF PIERRE MUGABO
PROFESSIONAL STATUS : MBCHB; MD; PHD
UNIVERSITY DEPARTMENT : SCHOOL OF PHARMACY
HOSPITAL/INSTITUTION : UNIVERSITY OF THE WESTERN CAPE
TELEPHONE NO : 021 959 3441
FAX NO : 021 959 3407
CELL PHONE NO : 082 202 3589
E-MAIL ADDRESS : PMUGABO@UWC.AC.ZA

SECTION 2: DETAILS OF SUB-INVESTIGATORS AT THE LOCAL SITE

NAMES OF SUB-INVESTIGATORS

Name : Dr M Bagwandeem
Name : Prof James Syce
Name :

SECTION 3: TITLE OF STUDY

SPONSOR'S PROTOCOL NO (if applicable): UWC 001

TITLE OF RESEARCH PROJECT:

A Pilot study on Mild to Moderate Asthmatic subjects to test the bronchodilatory effect of the herbal plant *Artemisia afra*.

SECTION 4: WHERE WILL THE RESEARCH BE CONDUCTED?

NAME OF HOSPITAL/INSTITUTION WHERE RESEARCH WILL BE CARRIED OUT

1. TYGERBERG HOSPITAL 2. STIKLAND HOSPITAL
3. KARL BREMER HOSPITAL 4. FACULTY OF HEALTH SCIENCES
5. OTHER 4 (PLEASE INDICATE BELOW)

Campus Health Centre

University of the Western Cape, Bellville

SECTION 5: INFORMATION ON THE TYPE OF TRIAL

1. SPONSORED TRIAL

2. SELF-INITIATED TRIAL **4**

NAME AND ADDRESS OF SPONSORING COMPANY AND CONTACT PERSON (if applicable)

Prof James Syce
School of Pharmacy
University of the Western Cape
Private bag X17
Bellville 7535

Telephone: 021 959 2192

Mobile: 082 202 3315

SECTION 6: SUMMARY OF PROTOCOL

SPECIFIC SCIENTIFIC OBJECTIVES

The primary objective of this study is to test whether *Artemisia afra* does indeed have any anti-asthmatic properties as claimed by traditional healers and whether a tablet dosage form would be similarly active as the traditional liquid dosage form. The major measure for the assessment of the anti-asthmatic effects will be improvement in FEV1. Secondary, the flavonoid luteolin present in the blood after ingestion of *Artemisia afra*, will be correlated with the the possible improvement of FEV1.

DESCRIPTION OF ALL MEDICINES INVOLVED IN THE TRIAL (including dosages, dose intervals and administration)

Patients will continue to take their regular asthma medication together with the study medication. 2 teaspoons dried leave product of *Artemisia afra* or the placebo, Rooibos tea, brewed in 200 ml boiled water will be taken twice daily for 12 weeks in phase A. After the first phase, the subjects will cross-over to the above mentioned plants in tablet form for another 12 weeks (phase B).

SUMMARY OF RESEARCH PLAN - including when the research will commence and over what period

This is a six months, randomised single blind placebo controlled study to investigate the bronchodilatory effect of *Artemisia afra* in 40 mild to moderate asthmatic subjects who are taking regular anti-asthmatic medication and comply with the inclusion and exclusion criteria.

The subjects who meet the criteria of the protocol and are accepted as subjects in the trial will be randomized into 2 groups to receive dried leave product of either *Artemisia afra* or the Placebo, Rooibos tea in phase A. Subjects will take 2 teaspoons leave product brewed in 200 ml boiled water twice a day for 3 months. The subjects will come for 7 visits during the study. Visit 0 and 1 must occur within 14 days of each other, all the other visits will be 30 days (\pm 3days) apart with visit 7 181 days after visit 1.

Subjects will be screened at visit 0, and if they meet the inclusion/exclusion criteria randomized for inclusion at visit 1. At visit 1 to 3 they will be issued with 1 month's supply of active or placebo dried leave product and at visit 4 to 6 they will receive active or placebo medication in tablet form. A diary card and instruction on the correct use of the medication will be issued with all above-mentioned visits. Lung function test will be done at visit 1, 4 and 7 to determine the FEV1. Subjects will receive a Peak Flow Meter at visit 1 to measure their peak flows daily in the morning and evening before taking any asthma medication, which will be noted on their diary cards. At each visit safety assessments will be done and blood samples will be drawn from the active subgroup at visit 4 and 7, always before the ingesting of the first dose for that day.

This trial will take place at the University of the Western Cape and will be starting in January 2004 until September 2004.

INCLUSION CRITERIA

AND

EXCLUSION CRITERIA

8 Inclusion criteria

To be enrolled, the following criteria have to be fulfilled at Visit 1:

17. Outpatients of either sex between 18 and 60 years.
18. Asthma diagnosed according to the ATS definition for at least 6 months prior to Visit 1.
19. Fixed daily use of any brand of IGCS for ≥ 30 days prior to Visit 1.
20. FEV1 ≥ 80 % of the predicted normal.
21. Subjects able to perform acceptable lung function test.
22. Ability to use a peak flow meter correctly.
23. No significant concomitant disease.
24. Signed informed consent. Consent must be obtained before any study-related procedures are conducted.

9 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

21. Asthma exacerbation within 4 weeks prior to Visit 1, as judged by the investigator.
22. A smoking history of ≥ 10 pack years.
23. Respiratory infection affecting the asthma within 1 month prior to Visit 1.
24. Other pulmonary disease.
25. Pregnancy of Breastfeeding
26. Females of childbearing age potential not using medically accepted contraceptive measures, as judged by the investigator.
27. Subjects who are scheduled to undergo hospitalisation due to surgery during the study.
28. Conditions associated with poor compliance, including alcohol or drug abuse.
29. Participation in a clinical study of any investigational product 1 month prior to visit 1 or during the study.
30. Subjects that would not normally use traditional herbal medicines.

SUMMARY OF PRE-CLINICAL DATA

Although various studies were done on the action of plant ingredients i.e. flavanoids such as luteolin, no pre-clinical data on the safety of the plant *Artemisia afra* is currently available.



SECTION 7: INFORMATION ON THE PATIENTS

NUMBER OF PATIENTS TO BE INCLUDED AT THIS SITE : 40

THE STATISTICAL/ANALYTICAL TOOL USED TO JUSTIFY THE NUMBER OF PATIENTS EXPECTED TO PARTICIPATE:

A sample size of 40 patients was chosen to achieve a power of 80% for concluding efficacy, assuming a mean FEV1 difference of 255 ml was achieved.

WHERE, HOW AND BY WHOM WILL PATIENTS BE RECRUITED?

Subjects will be recruited by the investigator on campus of the University of the Western Cape where more than 13 000 students are enrolled.

SECTION 9: INFORMATION ON STUDY MONITORING

WHAT MONITORING PROCEDURES WILL BE USED?

During the study an independent monitor will visit the investigational site to confirm that the facilities remain acceptable, that the investigational team is adhering to the protocol and that data are being accurately recorded in the CRFs. Source data verification (a comparison of the data in the CRF with the subjects laboratory test results and other source documents) will also be performed.

The trial will be monitored to insure patient safety, correct protocol procedure and that both SA GCP and ICH GCP is being followed. Authorised representatives of the Regulatory authority may visit the centre to perform inspections, including source data verification.

SECTION 10: GENERAL

HOW WILL THE RESEARCH BE FUNDED?

The study will be funded by UWC, as it is part of a post graduate programme.

TO WHOM WILL RESEARCH RESULTS BE MADE AVAILABLE?

The research results will be published in research journals and presented at conferences.

ANY OTHER INFORMATION WHICH MAY BE OF VALUE TO THE COMMITTEE

The submission of this protocol forms part of the research programme of a student. The topic of the thesis is titled: Guidelines for Clinical Trials of Traditional plant medicines – comparison with guidelines for allopathic medicine trials and application to the study of anti-asthma plant medicines. In addition this study forms part of an overall research programme, focused on the preparation and evaluation of plant medicine products.



APPENDIX 5

Response from Stellenbosch Institutional Review Board on submitted protocol





UNIVERSITEIT STELLENBOSCH-UNIVERSITY
jou kennisvennoot • your knowledge partner

03 March 2004

MAILED

Prof JA Syce
Department of Pharmacology
University of the Western Cape

Dear Prof Syce

PROTOCOL: UWC001

"A pilot study on mild to moderate asthmatic subjects to test the bronchodilatory effect of the herbal plant *artemisia afra*".

ETHICS REFERENCE NO: M04/02/009

RE: EVALUATION OF NEW APPLICATION

The Committee for Pharmaceutical Trials evaluated your application for the approval and registration of the above-mentioned project on 1 March 2004. The committee expressed its gratitude for the neat and concise manner in which the application was presented.

In principle the Committee is in agreement with the project, but cannot approve it until the following aspects have been attended to:

1. The Medicines Control Council's letter of approval for the study, including your participation in the study, should kindly be submitted.
2. It should be confirmed that you are the principal investigator, as it is indicated in the protocol synopsis that the principal investigator is Dr Mugabo.
3. A valid Certificate of Insurance should be submitted.
4. As the active agent may have an anti-inflammatory or other beneficial influence on asthma, it is recommended that the term "bronchodilator" be deleted from the study title. In the alternative, a daily challenge study with a 6 - 12 hour follow-up period should be considered.
5. It should be indicated whether the FEV₁ of more than 80% will be determined pre or post bronchodilator. Kindly note that if it is post bronchodilator, the FEV₁ inclusion criteria will fall away.
6. It is suggested that the inclusion criteria of FEV₁ >80% be lowered to 70% predicted as all individuals have to be on inhaled glucose corticosteroids.
7. The relative strength of the active substance and the placebo/comparator drug must be indicated.
8. In order to ensure validity and repeatability, the weight or volume of the active agent should be indicated in order to insure that individuals on the active drug are treated with dose equivalence. Furthermore, the time required for boiling herbal preparations has to be indicated as the strength of the extract as well as the volume which has to be ingested may be significant.
9. Detail on the manufacturing of the active substance and Rooibos tablets should be submitted.
10. The weight of the active substance and placebo which is contained in the manufactured tablets, should be indicated.
11. The methodology used to determine toxic levels of the flavonoid products should be indicated. The data or norms

04 March 2004 16:52

Page 1 of 3



Fakulteit Gesondheidswetenskappe · Faculty of Health Sciences



Verbind tot Optimale Gesondheid · Committed to Optimal Health
Afdeling Navorsingsontwikkeling en -steun · Division of Research Development and Support
Posbus/PO Box 19063 · Tygerberg 7605 · Suid-Afrika/South Africa
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available as to what represent a toxic level should be submitted.

12. In order to determine the drug's effect on the kidneys and vital organs, basic haematology and biochemical tests on blood and urine should be obtained at baseline and periodically repeated.

13. It is recommended that a pregnancy test should be conducted before the onset of the study and on completion thereof. The Patient Information Leaflet and Informed Consent Form should be amended accordingly.

14. The protocol should address the use of concomitant medications and whether drugs such as Theophylline, long acting β -agonists or anti leucotrienes are permissible.

15. The exclusion criteria should make mention of the use of systemic corticosteroids.

16. Under the heading "criteria for discontinuation" in the protocol, it is stated that systemic steroids used for worsening of asthma for more than ten days will lead to the exclusion of participants. This could lead to an unnecessary loss of participation. It is therefore suggested, provided that the notification of an adverse asthmatic event be clearly defined, patients may remain on the study under medical supervision even if on systemic steroid treatment.

17. With respect to the use or non-use of a nose clip when measuring FEV₁, it is suggested that one methodology be used in order to ensure consistency.

18. It should be indicated that the principal investigator will report serious adverse events to the Committee for Pharmaceutical Trials and Medicines Control Council within designated time lines.

19. In respect of the patient information leaflet and informed consent form,

19.1 if extended safety measures are put in place, a slightly larger blood sample than 10ml may be required;

19.2 it should be indicated that laboratory safety evaluations are being performed in the participant's best interest and are not to be done at his/her expense;

19.3 it should be indicated whether participants will be required to inform his/her general practitioners;

19.4 the procedure for reporting serious adverse events by participants to the treating physician, should be indicated;

19.5 the investigational procedures and summary of the schedule of events should be indicated;

19.6 applicable instructions as contained to the traditional healers' handbook, should be incorporated in the consent form;

19.7 the corrections, as indicated on the attached page(s) should be made; and

19.8 the Afrikaans and certified Xhosa versions should be submitted for approval.

20. The Committee for Pharmaceutical Trials is of the opinion that this is an important study and the foregoing comments for the improvement of the study are meant in a constructive manner.

Note: In keeping with international regulations, the Committee for Pharmaceutical Trials has passed a resolution whereby all trialists and staff are required to undergo accredited GCP training; a valid certificate of completion should be submitted to the committee. Training received during (site) initiation meetings is not regarded as being sufficient for this purpose. All participating investigators and study coordinators are expected to undergo accredited GCP training and proof of such training should be submitted within 6 months. As of June 2004, no new trials will be approved by the committee unless such documentation is provided. The Office for Pharmaceutical Trials may be contacted for information on appropriate GCP training offered.

It would be appreciated if you would submit these documents/amended documents as soon as possible in order to finalise the approval and registration of the project.

04 March 2004 17:01

Page 2 of 3



Fakulteit Gesondheidwetenskappe • Faculty of Health Sciences



Verbind tot Optimale Gesondheid • Committed to Optimal Health
Afdeling Navorsingsontwikkeling en -steun • Division of Research Development and Support

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Please mark all the corrections/amendments clearly in order to allow rapid scrutiny and appraisal.

A copy of the clinical trial/financial agreement will be sent to the Research Grants Administration Office.

Please quote the Ethics Reference Number on all correspondence henceforth.

Yours faithfully

MRS PETRO NEETHLING

OFFICE FOR PHARMACEUTICAL TRIALS

Tel: +27-(0)21-938 9075 / E-mail: pbern@sun.ac.za

Fax: +27-(0)21-933 6330



04 March 2004 16:52

Page 3 of 3



Fakulteit Gesondheidswetenskappe • Faculty of Health Sciences



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APPENDIX 6

Documentation for PharmaEthics Institutional Review Board –
Application for initial trial





University of the Western Cape

School of Pharmacy, Discipline Pharmacology

Private Bag X17, Bellville, 7535 South Africa

School of pharmacy: Tel: + 27 21 959-2190; Fax: +27 21 959 3407

Direct tel. line: +27 21 959 2192; Direct fax: +27 21 9591324; cell: 0822023315.

ref: 04JSL011

11 February 2004

Pharma-Ethics (Pty) Ltd
123 Amcor Rd
LYTTELTON MANOR 0157

Fax: +27 12 664 6355 e-mail: marzelle@pharma-ethics.co.za

Dear Ms Marzelle Haskins

PROTOCOL: UWC001
TITLE: A PILOT STUDY ON MILDE TO MODERATE ASTHMATIC SUBJECTS TO TEST THE BRONCHODILATORY EFFECT OF THE HERBAL PLANT ARTEMISIA AFRA.

Please find enclosed the application for the above-mention project for consideration by our Ethics committee. This is a project being done as part of our overall research programme on traditional plant medicines. The project is being done in the School of Pharmacy and Student Health Services of UWC and under the auspices of the South African Herbal Science and Medicines institute. The latter is made up of researchers from several departments at UWC. The application is also being submitted to MCC and the Committee for Pharmaceutical Trials of the University of Stellenbosch (who looks at it on behalf of the UWC Senate Research committee), because an additional aim of our research programme is to establish all the guidelines required for such clinical trials. This particular project also forms part of a Masters degree project.

We trust that we have completed all the required forms appropriately. If not please advise what else is required. Also, please kindly forward the bill for this submission to me.

Yours faithfully

Prof J A Syce
Deputy Dean Faculty of Natural Science and
Coordinator: School of Pharmacy Postgraduate Studies Programme

UWC: A Place of Quality, A Place to Grow
Prof James A Syce, School of Pharmacy, Discipline of Pharmacology, UWC

APPLICATION FORM FOR INITIAL TRIAL APPLICATION

PLEASE SUBMIT THE FOLLOWING WITH THIS APPLICATION:

- ◆ 09 Copies of the Application Form & Covering Letter (09 Copies)
- ◆ 08 Copies of the Protocol + Summary (08 Copies)
- ◆ 08 Copies of the Patient Informed Consent & Patient Information Sheet in English (PIC)
- ◆ 08 Copies of the Details of Financial Agreements with the Investigators
- ◆ 08 Copies of the Previous decisions by other Ethics Committees & Regulatory Authorities
- ◆ 08 Copies of the Motivation for the use of a Placebo Control (*Where applicable*)
- ◆ 04 Copies of the Investigator's Brochure (*Phase I, II & III studies*) / Approved Package Insert
- ◆ A Copy of each Investigator's CV (01 Copy of each document)
- ◆ A Copy of the MCC Letter of Approval/Application Letter to MCC (01 Copy)
- ◆ A Copy of the Certificate of Insurance (01 Copy)
- ◆ A diskette with the following information must accompany your application:
Protocol + Summary; Investigator's Brochure & PIC
- ◆ The fee for Ethics Committee review is: R5 500.00
(FIVE THOUSAND FIVE HUNDRED RAND – VAT inclusive)
- ◆ Cheques to be paid to Pharma-Ethics (Attention: Account's Department – Janine van der Merwe)

COMPANY DETAILS: School of Pharmacy, University of the Western Cape

APPLICANT'S NAME & POSITION: Prof J Syce (project leader)

PROTOCOL NUMBER: UWC 001

PROTOCOL TITLE: A Pilot study on Mild to Moderate Asthmatic subjects to test the bronchodilatory effect of the herbal plant *Artemisia afra*.

PRINCIPAL & SUB-/CO-INVESTIGATOR/S: Dr P Mugabo; Dr M Bagwandeen

ADDRESS WHERE STUDY IS TO BE PERFORMED: Student Health Centre, UWC Campus

COMPANY INSURANCE DETAILS: To follow

NUMBER OF PATIENTS TO BE INCLUDED: 40

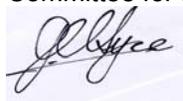
ARE THERE ANY INVASIVE PROCEDURES? No

IS THE INFORMED CONSENT / PATIENT INFORMATION SHEET IN THE RELEVANT LANGUAGES? YES / NO YES

MOTIVATION FOR THE USE OF PLACEBO: Normal treatment for asthma is continued, placebo will not have a negative effect on the disease.

PREVIOUS DECISION BY OTHER ETHICS COMMITTEES & REGULATORY AUTHORITIES:

MCC : awaiting response after recommendations were replied on
Committee for Pharmaceutical Trials: awaiting



Prof J Syce

11 February 2004

Date

APPENDIX 7

Response from PharmaEthics Institutional Review Board on submitted application



P.O. Box 786
IRENE
0062
Republic of South Africa



PHARMA-ETHICS

Pharma-Ethics (Pty) Ltd
Registration No. 99/13868/07
123 Amcor Road
LYTTTELTON MANOR 0157
Tel +27 (12) 664-7977/6
Fax +27 (12) 664-6355
e-mail: marzelle@pharma-ethics.co.za
e-mail: barbara@pharma-ethics.co.za

25 March 2004

FAXED

Prof J.A. Syce
University of the Western Cape
Department of Pharmacology
School of Pharmacy
Private Bag X17, BELLVILLE
7535
Fax: +27 21 9 59 1324

Dear Prof Syce,

PROTOCOL: UWC 001

A PILOT STUDY ON MILD TO MODERATE ASTHMATIC SUBJECTS TO TEST THE BRONCHODILATORY EFFECT OF THE HERBAL PLANT ARTEMISIA AFRA

ETHICS REFERENCE NO: 04030948

RE : APPLICATION FOR ETHICS COMMITTEE APPROVAL

Your application dated 11 February 2004 refers.

It was decided by Pharma-Ethics Research Ethics Committee that the above-mentioned application could not be approved due the following concerns:



PROTOCOL

- Page 2: Reference is made to the term "placebo". However, Rooibos tea is not a placebo treatment with no medicinal qualities and should therefore not be used as an inactive comparator.
- Page 3: In the statistical analysis no mention was made of the reduction in the use of rescue medication. Please explain why the reduction in use of rescue medication is considered as a study endpoint (page 2) but not considered as a variable in the primary efficacy analysis.
- Page 9 - STUDY PLAN AND PROCEDURES: The study is described as a single-blind cross-over design. The design described in the protocol is not crossover but parallel since the "placebo" group will remain on placebo and the active group will remain on active medication.
- Page 16 - STATISTICAL METHODS: There is no assumption about the standard deviation for the determination of sample size. Please comment.
- It is not clear why the study is only conducted on "Non-African" patients. Please comment. In addition a definition of what is considered "Non-African" for study purposes should be supplied.

Responses to the above concerns will be submitted to the committee meeting at the next meeting, and if found favorable will be approved or conditionally approved.

Our next meeting is scheduled for 1 April 2004. If you have your responses available by then, the committee will gladly take them into consideration.

Do not hesitate to contact me if you require any further information.

The above has been noted for the Ethics Committee information and records.

Chairperson: Dr E. Hammann
MBCIB DOH MPharmMed

Secretary: B. Marais

Directors: M. Haskins - BLC LLB (Managing), P.L. Marais - B Comm
O.B.W. Greef* - MBCIB MFGP(SA) MPharmMed FPPM (RCP) MD, G.M.M. Corken* - MPharm

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KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA /
SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE

Regards,



MRS MARZELLE HASKINS

For and on behalf of Pharma-Ethics



Chairperson: Dr E. Hammann
MBChB DOH MPharmMed

Directors: M. Haskins - BLC LLB (Managing), P.L. Marais - B Comm

O.B.W. Greef* - MBChB MFGP(SA) MPharmMed FPPM (RCP) MD, G.M.M. Corken* - MPharm

Z. A. ACRI'ON

* Non-Ethics 0000600 (710) 181000110

Secretary: B. Marais

01101 4007 1100102

Dear Mrs Haskins

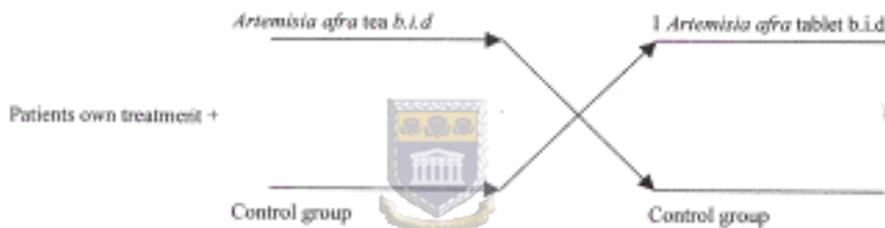
PROTOCOL: UWC 001
A PILOT STUDY ON MILD TO MODERATE ASTHMATIC SUBJECTS TO TEST THE BRONCHODILATORY EFFECT OF THE HERBAL PLANT *ARTEMISIA AFRA*.

ETHICS REFERENCE NO: 04030948

REPLY REGARDING RECOMMENDATIONS

Thank you for the prompt review of the above-mentioned protocol. Herewith our response to your concerns:

1. Page 2: In view of the fact that Rooibos tea may have a medicinal effect, the use of this tea as a placebo will have to be disposed of. It is therefor suggested that the study will be conducted as a proof of concept study and the placebo group replaced with a control group (no extra study medication). It will then be a controlled, open label, randomised cross-over study in subjects with stable asthma with or without maintenance treatment.
2. Page 3: The reduction in medication as a study endpoint refers to **maintenance** medication (Inhaled Glucocorticosteroids) and not **rescue** medication.
3. Page 9: The study plan diagram was incorrectly labeled. Following question 1 (page 2), it should now look as follows:



4. Page 16: Calculations based on the desire to achieve a 255ml difference with an 80% power, a sample size of 40 randomised patients will be required. A Standard deviation of 285 was obtained from previous studies done on the bronchodilatory response of salbutamol.
5. Page 2: In this study Non-African patients are **excluded (not included)** in order to capture the "belief" aspect of traditional herbal medicine use. In this contents Non-African patients is taken to mean "people that would not normally take of believe in the effectiveness of traditional herbal medicine".

I do hope that the above explanations will answer your queries and that the study will be considered favourably at your next meeting.

Regards

Prof James Syce

P.O. Box 786
IRENE
0062
Republic of South Africa



PHARMA-ETHICS

Pharma-Ethics (Pty) Ltd
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e-mail: barbara@pharma-ethics.co.za

26 April 2004

FAXED

Prof J.A. Syce
University of the Western Cape
Department of Pharmacology
School of Pharmacy
Private Bag X17, BELLVILLE
7535
Fax: +27 21 9 59 1324

Dear Prof Syce,

PROTOCOL: UWC 001

A PILOT STUDY ON MILD TO MODERATE ASTHMATIC SUBJECTS TO TEST THE BRONCHODILATORY EFFECT OF THE HERBAL PLANT ARTEMISIA AFRA

ETHICS REFERENCE NO: 04030948

RE : APPLICATION FOR ETHICS COMMITTEE APPROVAL

Your response dated 29 March 2004 refers.

Please note that the Ethics Committee can still not approve the above-mentioned protocol due to the following reasons:

- Your response to query no. 2 specified that reduction in medication as a study endpoint refers to maintenance anti-asthma medication and not rescue medication. We agree that we quoted the protocol incorrectly, however normally efficacy should be shown mainly by reduction in rescue medication and reduction of maintenance to a lesser extent. Whatever the case may be, the initial question referred to the fact that in the primary efficacy analysis, no mention was made to the reduction of MEDICATION even though it is considered as a study endpoint.
- In addition, the sample size seems to refer to a "lung function" measurement, whereas the primary efficacy is reduction in medication.

It was the committee's recommendation that the above-mentioned comments should be considered and that a new protocol should be submitted to the Ethics Committee.

The above has been noted for the Ethics Committee information and records.

***KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA /
SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE***

Regards,

MRS MARZELLE HASKINS

For and on behalf of Pharma-Ethics

Chairperson: Dr E. Hammann
MBChB DOH MPharmMed

Secretary: B. Marais

Directors: M. Haskins - BLC LLB (Managing), P.L. Marais - B Comm

O.B.W. Greeff* - MBChB MFGP(SA) MPharmMed FPPM (RCP) MD, G.M.M. Corken* - MPharm

11 APR 2004 13:56

11 APR 2004 13:56

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