

## **Herbal medicine research and global health: an ethical analysis**

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### **Introduction**

Traditional herbal medicines are naturally occurring, plant-derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing practices. Traditional herbal medicines are getting significant attention in global health debates. In China, traditional herbal medicine played a prominent role in the strategy to contain and treat severe acute respiratory syndrome (SARS).<sup>1</sup> Eighty per cent of African populations use some form of traditional herbal medicine,<sup>2,3</sup> and the worldwide annual market for these products approaches US\$ 60 billion.<sup>2</sup> Many hope traditional herbal medicine research will play a critical role in global health. China, India, Nigeria, the United States of America (USA) and WHO have all made substantial research investments in traditional herbal medicines.<sup>2</sup> Industry has also invested millions of US dollars looking for promising medicinal herbs and novel chemical compounds.<sup>4,5</sup> This is still a relatively modest investment compared to the overall pharmaceutical industry; however, it raises interesting ethical questions, some of which are not faced in more conventional drug development.

As attention and public funding for international traditional herbal medicine research collaborations grows, more detailed analysis of ethical issues in this research is warranted. Scant literature has addressed selected issues such as informed consent and independent review related to traditional herbal medicine research.<sup>6,7</sup> Here we apply a practical, comprehensive and widely accepted ethical framework to international traditional herbal medicine research.<sup>8</sup> We examine in detail difficult questions related to social value, scientific validity and favourable risk–benefit ratio. We conclude with implications for future research in this area, focusing on the importance of collaborative partnership.

### **Case**

A government agency from a developed country is conducting an HIV-treatment trial in Africa. A traditional herbal medicine, Africa Flower, has been used for decades to treat wasting symptoms associated with HIV. Local traditional medicine healers believe Africa Flower is an effective antiviral. It is already widely used for immune boosting in AIDS. In vitro pharmacokinetic studies suggest potential interference with vaccines, and animal models show liver toxicity at very high doses. There are no systemic side-effects reported for humans in the literature. A few case series have shown mixed results. Local leaders are requesting the government agency conduct a large, randomized controlled trial (RCT) of Africa Flower to test its efficacy as a novel adjunctive therapy to slow progression to AIDS.

## Ethical framework

Cases like these present challenging questions related to the role of traditional herbal medicines in public health. In general, international research on traditional herbal medicines should be subject to the same ethical requirements as all research related to human subjects.<sup>9</sup> An ethical framework previously outlined by Emanuel et al. and revised for international research<sup>8</sup> offers a useful starting point for thinking about the ethics of international traditional herbal medicine research. This framework includes eight ethical requirements for clinical research (Table 1).<sup>8</sup> These ethical requirements are universal and comprehensive but must be adapted to the particular social context in which the research is implemented.<sup>8</sup> Of these, fair subject selection, independent review, informed consent, and respect for enrolled subjects have been discussed previously in the literature on the ethics of global health research and raise few issues unique to international traditional herbal medicine research.<sup>8</sup> However, social value, scientific validity, and favourable risk–benefit ratio raise specific challenges in international herbal medicine research that have not been adequately discussed.

**Table 1. A comprehensive framework for research ethics**

Ethical requirement	Definition
Collaborative partnership	Research leadership must include bilateral representation based on mutual respect between equal partners with community advice. It includes a responsibility to invest in the scientific training and capacity-building for ongoing research in a host country where such resources are not well developed.
Social value	Knowledge gained from the research should have the potential to lead to new generalizable knowledge or improvements in health. Partners should specify in advance to whom benefits will accrue and in what way.
Scientific validity	Research should be designed to produce beneficial and generalizable knowledge. This includes designing research so that it can be feasibly implemented in the settings where it will be conducted.
Fair subject selection	Subjects should be selected on the basis of scientific importance, not based on convenience, vulnerability or bias.
Favourable risk–benefit ratio	The potential benefits of individual participation should outweigh the risks of participation. Benefits to the community or population being studied should also be optimized. Compelling societal benefit can justify risks to individuals in certain circumstances.
Independent review	To maintain the integrity of the research, bodies not tied to the investigators must agree that the risks and potential benefits of the research are justified.
Informed consent	Investigators must obtain valid permission for study participation from subjects in a manner that is sensitive to the cultural context in which the study is conducted.
Respect for subjects	Researchers should have a plan for how the research results will be disseminated; ensuring participants know their right to withdraw, and monitoring the research for relevant adverse

## Social value

All research should hold the potential to achieve social value. Different entities may view the social value of traditional medicine research differently. Public-health officials are often eager to define the safety and effectiveness of herbal medicines for conditions such as malaria.<sup>3</sup> Conversely, harm can arise with the unscrupulous use of herbs such as Africa potato (various *Hypoxis* species).<sup>7</sup> While some claim that such medicines have “stood the test of time”, they nonetheless pose serious challenges to investigators and regulators from developed countries, in which standards of proof are closely linked to proven efficacy in RCTs. Accordingly, there has been a serious investment in herbal medicine research by public-health bodies in many countries. China recently launched a safety research programme focusing on herbal medicine injections from traditional Chinese medicine.<sup>10</sup> South Africa recently included the need for investigating traditional medicines within its national drug policy.<sup>11</sup>

In the USA, the National Center for Complementary and Alternative Medicine at the National Institutes of Health spent approximately US\$ 33 million on herbal medicines in fiscal year 2005; in 2004 the National Cancer Institute committed nearly US\$ 89 million to studying a range of traditional therapies.<sup>12</sup> While this scale of investment pales in comparison to the total research and development expenses of the pharmaceutical industry, it nevertheless reflects genuine public, industry and governmental interest in this area.

While public-health entities may be concerned with defining the risks and benefits of herbal medicines already in use, entrepreneurs and corporations hope herbal medicines may yield immediate returns from herbal medicine sales, or yield clues to promising chemical compounds for future pharmaceutical development. They test individual herbs, or their components, analysed in state-of-the-art high-throughput screening systems, hoping to isolate therapeutic phytochemicals or biologically active functional components. In 2006, Novartis reported that it would invest over US\$ 100 million to investigate traditional medicine in Shanghai alone.<sup>4,5</sup>

Nongovernmental organizations may be primarily interested in preserving indigenous medical knowledge. One such organization, the Association for the Promotion of Traditional Medicine (PROMETRA), based in Dakar, Senegal, is “dedicated to preserving and restoring African traditional medicine and indigenous science”.<sup>13</sup> Governments in developing countries may want to use traditional herbal medicine research to expand the influence of their culture’s indigenous herbal practices in the global health-care market. For instance, Nigeria’s president recently established a national committee on traditional medicine with the expressed desire to boost Nigeria’s market share of traditional medicine.<sup>14</sup> In developed countries, the “need” for this research may be to protect the public.

The perceived need for the research may justifiably differ across countries, but without some basic agreement on the primary source of social value for the research it may be difficult to judge its ultimate impact. In the Africa Flower case above, before agreements to study a herbal medicine are decided, partners must fully discuss potential differences about the perceived “need” for the research through public forums or structured debates. Based on these frank discussions, partners can assess whether the social values of partner countries are sufficiently compatible to warrant a research partnership.

## Scientific validity

Part of ensuring the social value of research includes devising and implementing sound science. Although international collaborative research on herbal medicine is no exception, discussing scientific validity as an ethical requirement raises some specific challenges, including the meaning of scientific validity, establishing inclusion and exclusion criteria, using appropriate outcome measures, and determining appropriate study designs.

### Balancing internal and external validity

Building a valid basis for knowledge in herbal medicine will require balancing two aspects of scientific validity: internal and external validity.<sup>15</sup> Internal validity means the research must reliably test hypothesized relationships between an intervention and an outcome under controlled conditions. Internally valid research will typically try to answer a focused research question that is salient within the vocabulary and methods of the scientific community at the time the research is conducted. External validity refers to the applicability of the research results to a target population outside the experimental conditions of the research study. External validity must always be weighed against the need for rigorous internally valid research.

This tension between internal and external validity can be illustrated by a recent herbal medicine trial of *Echinacea angustifolia* extract for prevention of parainfluenza virus infection.<sup>16</sup> The study was conducted under rigorous experimental conditions, but many herbalists pointed out that study conditions did not sufficiently reflect how these medicines are actually used. Null treatment trial results like these prompt questions about the external validity (i.e. value and meaning) of the research. Was the herbal medicine truly ineffective, or did the experiment not reflect the herb's use in "real-world" practice? In herbal medicine there are often huge variations in the way in which the medicines are used in herbalist practice, including herb source, preparation, dose and indication. Because traditional herbal medicine practitioners may be unregulated and their products lacking in standardization, it may be difficult to generalize the results from a formal, structured and highly monitored trial to what will happen in the widespread dissemination of the herbal medicine. Nevertheless, herbal medicine research must endeavour to achieve a balance between internal and external validity.

### Inclusion and exclusion criteria

To ensure that research results are externally valid, the inclusion and exclusion criteria for research participation should fit with existing diagnostic categories in the target population specified by the research question. However, conceptualizations of health and illness can vary across medical systems and populations, making agreement on valid inclusion and exclusion criteria for international herbal medicine research collaborations more difficult to achieve.

During the SARS epidemic, traditional Chinese medicine (TCM) practitioners involved in the care of SARS patients characterized patients based on nosological categories derived from TCM including "deficiency of chi and yin" as well as "stagnation of pathogenic phlegm".<sup>17</sup> Designing clinical trials using these kinds of TCM categories as inclusion criteria would require significant additional effort and biomedical flexibility to implement. If one wanted to test whether TCM works for populations in south-east Asia affected by a SARS-like illness, adapting the science to include traditional diagnostic categories may be critical for its ultimate external validity.

If American researchers want to test a herb's effects on heart failure, they might use the New York Heart Association classification as part of the inclusion/exclusion criteria. However, this classification makes little sense from a TCM perspective, in which heart failure may be viewed primarily as either a heart *yang chi* deficiency or a kidney *yang* deficiency.<sup>18</sup> TCM practitioners may prefer to categorize patients based on pulses, tongue examination, and other elements of traditional diagnosis. Investigators have simultaneously used both biomedical entry criteria and stratified for TCM diagnosis.<sup>19</sup> Such an approach is scientifically ideal because of its ability to maximize the external validity of results.

## Valid outcome measures

International herbal medicine research must use outcome measures that accurately capture the effects conferred by herbal medicines. However, constructs such as "physical functioning" or "psychological well-being" measured by the SF-36 quality of life instrument make little sense within the terminology and ideas of TCM.<sup>20</sup> Therefore to accurately measure a TCM herb's effects on quality of life, some investigators have constructed and validated analogous measures that more faithfully detect the effects of TCM interventions that make sense within that healing tradition.<sup>20,21</sup> Ideally, when new measures are introduced, they should overlap with existing outcome measures, so that the research can adequately contribute to the existing body of knowledge.

## Determining research design

While it is generally agreed that all human subjects research must maintain valid study designs, questions arise about the characteristics of a valid research design. Two extreme positions are often defended. At one extreme, some researchers trained in biomedical methods of clinical investigation argue that the *only* valid source of knowledge regarding clinical efficacy must come from one type of research design, the randomized double blind, placebo-controlled trial. They argue that any deviations from this gold standard of scientific validity amount to worthless science.

At the other extreme, critics of biomedical research conducted on traditional medicines charge that attempts to evaluate traditional therapies with biomedical methodologies may fail to generate true knowledge, since that knowledge itself depends on a scientific vocabulary that only makes sense from within the concepts of biomedicine.<sup>22-24</sup> They worry that "standard notions of ... experimental design criteria represent an imperialistic 'western' mode of thinking".<sup>22,24</sup>

Research on herbal medicines should typically employ experimental research designs such as the RCT. Even if research tools (including the RCT) are imperfect,<sup>25</sup> they are thus far the best methods we have for furthering our knowledge.<sup>9,15</sup> Consider how RCT designs could be implemented in TCM, in which treatments are individualized to patients, often incorporating several, or even dozens, of herbs in a customized preparation. Despite these complexities, investigators have successfully adapted double-blind RCT designs to complex individually tailored Chinese herbs. Bensoussan et al. conducted a three-arm trial in which they tested the comparative clinical efficacy of standard complex herbal medicines, customized therapy and placebo.<sup>26</sup> Standard and customized therapy were comparably beneficial as compared to placebo. In other instances, cluster RCTs can allow for practitioner variability, while still rigorously testing the efficacy of a therapeutic approach. In cross-cultural settings, researchers cannot merely adopt alternative designs in an ad hoc manner, but must reflect on and refine



their research question, and find a design that best answers the research question within the given cultural context.

In recent years, growing attention has been paid to a group of additional important ethical issues surrounding publication bias, financial conflicts of interest, and clinical trial registries. In the arena of traditional herbal medicine, these same issues apply, and when cross-cultural differences exist in the definitions of valid science, as is the case in traditional herbal medicine research, these questions compound. For instance, until recently, there was a tendency to see only positive studies published in China. It is, therefore, critically important to the long-term scientific credibility of international traditional herbal medicine research that, at the outset, partners agree about the standards of scientific conduct, the disclosure of financial relationships, registration of clinical trials, and adequate reporting of trial results.

## **Favourable risk–benefit ratio**

In international herbal medicine research, several practical challenges arise in making accurate risk–benefit determinations. Typically, in American pharmaceutical development, a step-wise process of drug testing occurs – a compound is isolated, tested in tissue cultures and animals, and then investigated in phase 1, 2 and 3 clinical trials. However, herbal medicines are already in widespread use, are often used in combination, and are drawn from plant sources with their own variability in species, growing conditions and biologically active constituents. They often come into use by a process of trial and error, or over centuries. Accordingly, in clinical herbal medicine research there is rarely a strong preclinical basis for dosing, and there are significant looming questions about product purity, quality, chemical stability and active constituents at the time herbal medicine trials are proposed.<sup>[27,28](#)</sup>

Initiating large-scale research trials in such circumstances raises questions about whether the risks and benefits of research participation can be accurately ascertained. Those reviewing protocols should factor in the uncertainty associated with product variability in determining whether a herbal medicine trial has a favourable risk–benefit ratio. However, protocol reviewers (i.e. institutional review boards) should not presume that because they are personally unfamiliar with a herbal preparation that there is no credible or valuable background evidence regarding safety and potential efficacy. While researchers should provide such information in protocol materials, reviewers must remain aware of the role their own lack of familiarity may play in their ultimate judgements of risks and benefits of the research.

Researchers increasingly agree that it is important to establish a rational basis for dosing and standardization of biologically active compounds before conducting large-scale treatment trials.<sup>[29,30](#)</sup> These efforts can improve investigators' ability to assess the risks and benefits of participation in large-scale herbal medicine trials. Likewise, more rigorous monitoring of adverse events and standardized reporting of research results for both safety and efficacy data will improve long-term efforts to enhance risk–benefit ratio determination for trial participation.<sup>[31](#)</sup>

Cultural factors also may influence judgements of the risks and benefits in herbal medicine research. For instance, a cultural familiarity with many traditional Chinese herbal medicines in China may promote a familiarity bias, accepting a widespread cultural assumption of safety, based on the historical use of herbal medicines.<sup>[32](#)</sup> There may also be a cultural difference in emphasis placed on standardized adverse events reporting in China.<sup>[33](#)</sup> These cultural differences make achieving agreed-upon standards of favourable risk–benefit ratio more difficult. In order for international collaborative

herbal medicine research to achieve its objectives, it will be important to establish standards of evidence for demonstration of safety before conducting large-scale clinical trials evaluating the efficacy of herbal medicines.

## **Improving science through collaborative partnership**

How can international collaborative herbal medicine trials achieve the ethical requirements outlined above? Collaborative partnership, the first requirement for international research ethics, provides both the rationale and the context for achieving appropriate application of the other ethical requirements. Partners in these collaborations must share vocabulary for all the requirements, especially for social value, scientific validity, and favourable risk–benefit ratio. How can agreed-upon language be achieved? As illustrated here, these challenges are significant. In the case presented earlier, investigators should have reservations about implementing a large-scale clinical trial for Africa Flower. Nevertheless, the local interest in this substance may be valid and deserve some additional preliminary investigation. Collaborative partnership displays a commitment by all parties in international research agreements to work together for common language and goals.

To achieve collaborative partnership, parties can engage in structured methods of democratic deliberation to devise shared language and concepts for research. These methods have been used to bring different parties together in a safe and collegial process of decision-making.<sup>34</sup> Over time, collaborations could “cross-train” basic and clinical investigators to more fully appreciate the concepts and practices of the traditional herbal medicine traditions, and developing host countries would need to develop the basic literacy, knowledge and skills among traditional medicine practitioners so that they see the value of rigorous clinical research.<sup>2</sup> With a sustained investment like this, it will become increasingly possible to conduct sound international scientific investigation on traditional herbal medicine. Furthermore, sustainable collaborative research partnerships would benefit from robust and independent adverse-event reporting systems for herbal medicines so that the risk–benefit ratio for herbal medicine research can be more clearly defined.

Ethical challenges in international traditional herbal medicine call for a comprehensive framework. Addressing these challenges requires collaborative partnership that implements sound research designs. So envisioned, international herbal medicine research can contribute to global health. ■

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