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Unique Aspects of Herbal Whole System Research

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Abstract

Introduction—Whole systems of healthcare offer unique methodological and theoretical challenges for researchers. Herbalism has its own set of methodological and philosophical research issues, which are beyond those presented for whole system research, in general.

Methods—An International Society for Complementary Medicine Research (ISCMR) workshop was presented on, “Challenges in Herbal Whole Systems Research”. Starting from a definition of herbalism the most important challenges to herbal whole system research (HWSR) were elicited with inputs from both the workshop presenters and the audience.

Results—Five major challenges unique to herbal whole systems research were identified: (1) Defining herbalists and herbalism; (2) role of natural products industry in herbal research; (3) designing placebos and delivering active herbal treatments as are given by herbalists; (4) researching the herb as a living entity; and (5) designing trials to investigate and develop multi-component herbal therapies.

Conclusions—To design studies of herbalism requires unique methods and theoretical frameworks. Solutions to these methodological challenges need to be addressed to conduct research that examines herbal systems of medicine versus conducting trials on individual herbs given out of their original therapeutic context.

Keywords

Whole Systems; Herbalism; Research Methodology

INTRODUCTION

Complementary and alternative medicine (CAM) is partially composed of systems of healthcare such as Traditional Chinese Medicine (TCM) and naturopathy. These systems of healthcare are made up of complex interventions, e.g. diet, exercise, herbs and supplements. These whole systems also have their own methods of diagnosis and prognosis as well as disease classifications and causation that are often distinct from Western Biomedicine. Researching and even defining alternative whole systems of healthcare has offered numerous methodological and theoretical challenges. A definition of whole system research has been proposed by groups of CAM research experts¹ as have various methodological challenges² that apply to whole systems in general. A few alternative systems of medicine such as naturopathy³ and acupuncture⁴ have also been explored for some of their unique

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methodological challenges. However, herbalism or herbal remedies which constitute one of the most commonly used healing modalities in the world have not been examined for unique issues that are involved in researching this system of healing.

The International Congress of Complementary Research (CMR) sponsored by the Centre for Complementary Medicine Research at the Technical University in Germany and The International Society for Complementary Medicine Research (ISCMR) was held in München, Germany May 11–13, 2007. A pre-conference CMR workshop, devoted to examining unique methodological issues and entitled, “Challenges in Herbal Whole Systems Research”, was sponsored by ISCMR. The current paper is a review and discussion of methodological issues and possible solutions raised by both the speakers and audience discussion about conducting herbal whole systems research (HWSR). This paper addresses five of the most prominent challenges unique to HWSR and possible answers to these challenges arranged from the more general issues to the most specific topics. We first present a section describing the conceptual parameters around HWSR which is followed by two sections on the pragmatics of conducting research, and we then conclude with possible qualitative and quantitative research methodologies for HWSR.

Defining Herbalists and Herbalism

One major challenge unique to herbal whole systems research is identifying and defining the terms herbalist and herbalism. As many countries, states and provinces have no clear certification or licensure for herbal practitioners, researchers are often left with an eclectic mix of practitioners who could be herbalists but practice in such different fashions as to make operationalization and definition of the term difficult and perhaps even meaningless. Despite these challenges, we would propose that a clear definition of herbalist and herbalism is possible and necessary. We suggest the following as starting parameters in arriving at a meaningful classification of an herbalist.

An herbalist can be defined as a practitioner who uses medicinal herbs as a primary modality to treat patients or clients. An herbalist could also use other therapies such as diet, pharmaceuticals or meditation as a complement to herbal treatments. These other modalities would either not be considered the most potent aspect of the therapeutic intervention or not be the most utilized aspect for treating specific medical conditions or indications. Further, practitioners can either work full time as herbalists or use herbs only with selected conditions or indications. “Ideally”, an herbalist is someone whose main life vocation involves working with medicinal plants and who uses herbs as “the” primary modality to treat patients or clients.

In addition, herbal practitioners self-identify as herbalists even if they are trained or are licensed within another professional category, e.g. MDs, naturopathy or TCM. We would further recommend comparing self-report of herbalists to actual clinical practice patterns, as actual clinical observations may not confirm self-report. To help discern discrepancies between self-report and actual observations, having clear practice guidelines *a priori* about the proportion, amount and frequency of herbal use as part of practice would help to clarify the amount of herbalism practiced.

The definition of herbalists can generally be divided into two categories, “lay” and “professional”. Making the distinction between these two categories needs to be tailored to each geographic region as herbal traditions and training differ greatly across countries and even local jurisdictions. One useful way of identifying the professional herbalist is to use existing certifications, professional designations and licensure for herbalists available in the geographical area of interest. All other practitioners meeting the general definition of herbalist that do not have a professional designate would be, by default, considered lay herbalists. For example, in the United States (US) one could use professional membership in the American

Herbalist Guild (AHG) as the study's definition of "professional" herbalist. Although professional AHG members come from various traditions and educational pathways including apprenticeships without formal schooling, shamanistic training and four-year classroom degrees in herbalism, all professional AHG members must go through an extensive vetting process conducted by other professional AHG members before receiving the professional distinction.⁵ In the United Kingdom (UK) one could use membership in one of the main professional associations, the National Institute of Medical Herbalists (NIMH). For example, in contrast to the more eclectic AHG professional members, NIMH members undergo a pre-determined training program before they can register as qualified medical herbalists that includes 500 hours of clinical training and at least three years at a school accredited by the NIMH Accreditation Board.⁶ Clearly membership in other professional organizations, such as licensed naturopathic physicians, or MDs who receive advanced phytomedical training like the Swiss Medical Society for Phytotherapy, could be used depending on the goals of the research.

Over-the-counter (OTC) herbal preparations play an important role for the general public and for those herbalists who have no possibility to carry their own products and will thus need to send clients to stores to purchase herbs. In our definition of herbalism, the OTC herbal use prescribed by an herbalist is part of a whole system of herbalism. This distinction is of particular use when looking at prevalence studies of herbal whole systems where a product an herbalist has prescribed may be counted twice: once as the product and once as a visit to the herbalist, leading to overestimates of herbals and herbalism.

Role of Natural Products Industry in Herbal Research

One major challenge of HWSR is the availability and development of herbal products for research studies. Modern clinical studies demand immense structural, logistical, and of course financial capacities from the involved research team. Modern drug research is governed by a set of good practice standards such as good clinical practice (GCP), which increases the performance barrier substantially. HWSR will for the most part be performed as an investigator driven study. Such studies are possibly bound to a less rigid framework than studies for drug licensing purposes but nevertheless many challenges similar to drug studies remain.

One such possible challenge comes up if specific parts of the research project have to be outsourced to specialists; for example, the production of the herbal research material is performed by a compounding pharmacy or an herb company. A specific research idea demands a specific herbal formula, presented in a suitable delivery system (tablet, capsule, tea bag, syrup, decoction, ointment, etc.). In a randomized double-blind setup, there is also the necessity for developing and producing a suitable placebo. Such a feasible randomization procedure might also demand special packaging. In short, novel research ideas imply the production of a novel product.

Herbal companies willing to participate in research have to openly communicate with the research team. The questions of property rights, of patents, and of funding have to be openly discussed. Production of the clinical material, in order to fulfill optimal criteria, has to comply with good quality procedures including good manufacturing practices (GMP) and good laboratory practices (GLP). Quality parameters, identity parameters and correct botanical identification are mandatory. Furthermore, stability of placebo and verum (until end of the study) have to be guaranteed and monitored with stability tests that first might have to be developed. Toxicity tests and pharmacokinetics studies may also be needed. If the intended research product is a new formula, the establishment of these procedures is a tremendous investment even before the start of clinical studies.

According to the regulations of the respective country, it might be necessary to file product information with the appropriate authorities and obtain the necessary ethical and regulatory approvals. Of course the international standards of biomedical research should be observed in any case (e.g., Declaration of Helsinki). These standards are also laid down in local laws about biomedical research with human subjects. Also, proper documentation of the herbal product is mandatory. As guidance the recommendations of the International Conference on Harmonisation of Technical Requirements For Registration Of Pharmaceuticals For Human Use (ICH) Brochure⁷ can be adapted for HWSR; especially important in this context are the specifications for an Investigator's Brochure.

Herbal researchers should be aware that an herbal company may not be willing or even able to provide the information necessary to complete regulatory paperwork such as an Investigator's Brochure that could be required to conduct herbal research depending on locale. Listed here is some of the information that researchers may need to ask an herbal company to provide: (1) certificate of analysis (CoA) of both the original source material for the herb product (raw herb) and the finished product, e.g., tablet; (2) detailed flowchart and instructions on how the raw material is compounded; (3) information including pharmacopeia references to any solvents, additives etc. that are used in the manufacturing of the herbal product(s); (4) where, e.g., countries, and how, e.g., organic farming, the original plant was grown; (5) quality control procedures used in the manufacture of the herbal product; (6) the existence of an Investigator's Brochure; (7) any toxicology, stability or dosing information available on the product; and (8) if the product standardized to a particular constituent including data on batch-to-batch variability and standardization methods. Researchers should also be aware that many herbal companies distribute but do not make the herbal product and thus must go to the manufacturing company to obtain information about their product. This, of course adds another layer of potential difficulty in obtaining accurate information needed for researching herbal products.

In parallel with the increasing involvement of an herbal enterprise in the research process new challenges will surface. There could be the potential for conflicts between research team and company. For instance, there may be conflict regarding the aim and performance of the study. Best practice recommends that the research team clearly define the design of the study, and have a policy statement or service contract with the company to ensure the independence of the research team and any data generated. Researchers may also find it difficult to obtain external grants depending on the level of involvement of the herbal company. In addition, in the cases where the clinical trial is funded by herbal industry the same ethical stances as outlined in Good Clinical Practice (GCP) in research for pharmaceuticals should apply to herbal research. These allow reasonable payments to clinicians, subject to disclosure of any possible conflicts of interest. The potential to provide incentives to clinicians to recruit should be limited as any payments should be based on the cost of inputs and should not be made to individuals but to their host organization. In addition, any research grants from herbal companies need to be made to the researcher's institution, not to individual researchers, and should be posted on publicly available website(s) which will later include the research results including being posted on the Clinical Trials Registry. This later suggestion helps to ensure that unfavorable results will more likely be published or disclosed. Also, patients should receive full disclosure as to who benefits from the research and payment of expenses to patients involved in research.^{8,9} Even if herbal researchers receive no or limited resources from an herbal company, researchers still need to fully disclose to research participants who benefits from the research, i.e., the company that made the herbal product, to ensure appropriate ethical standards.

Addressing issues around the manufacture of herbal research products and its attendant regulatory requirements is of essential importance to the future of conducting HWSR. Novel methods of maximizing benefits to herbal companies, ensuring quality of products and

increasing the variety of herbal products available for herbal research while minimizing regulatory and cost requirements to both parties are needed. Possible solutions to some of the problems proposed could include forming close relationships between a research team and a particular herbal company to create and regulate a line of herbal products for research. The herbal company could aim to have these herbal remedies marketed to hospital pharmacies and physician offices, opening up new markets and justifying the additional expense.

Another idea would be the creation of a small business that provides consulting services and processes paperwork to satisfy regulatory requirements, e.g., investigational new drug (IND) application for herbal products. The regulatory consulting company could then offer regulatory paperwork and other legal requirements to multiple researchers for the same herbal products, although the herbal product would need to be tested for different indications or in different populations. Also, the botanical IND would need to be customized for each investigator's particular need while keeping the common elements such as the herbal manufacturing data. The combined fees of several researchers could help to offset costs to both the small herbal regulatory consulting company and to herbal researchers. In a similar fashion, herbal companies could also choose to work as service providers and process regulatory paperwork and other requirements for their products for an added fee.

Placebos for Herbal Medicine Research

The placebo arm in a randomized clinical trial (RCT) allows for single or double blinding that reduces bias, increases the internal rigor of a clinical trial¹⁰ and enables an assessment of both the specific and the non-specific effects of an herbal intervention. In many CAM therapies it is simply not possible to create a convincing placebo but in herbal medicine it is both possible and desirable.

There are significant difficulties in developing herbal placebos. Crude herbs have bulk, color, aroma and taste that are difficult to mimic with therapeutically inert ingredients. Herbs can be processed to make extracts, concentrated powders or granules which can then be prepared as tablets or capsules to facilitate the development of a convincing placebo,^{11,12} but for many practitioners, this does not reflect their normal clinical practice. In these instances the generalizability of the research has been compromised by the desire for internal rigor within an RCT. The challenge for research into the practice (as opposed to the OTC consumption) of herbal medicine is to evaluate what practitioners actually do and not to change the practice in order to fit into an acceptable research design.

Two pieces of research into Chinese herbal medicine (CHM) demonstrate these quandaries. A trial¹² treating irritable bowel syndrome (IBS) used encapsulated herbal powders with a placebo of dyed starch. This allowed both individuated and standardized prescriptions to be compared with a convincing placebo. However, despite the positive outcome of the study, many would argue its use of encapsulated concentrated powders lacks the synergy and resultant potency of boiled up herbs and does not reflect the best practice of CHM.

By contrast an eczema trial¹³ compared active and placebo decoctions of standardized herbal "teabags". The double blind cross-over design meant that the placebo teabag had to have a convincingly strong taste and aroma to compare with the active herbs. The placebo contained strong tasting pharmacologically active herbs like hops (*Humulus lupulus*), which provided convincing bulk and taste but threatened the therapeutic inertia and the ethical acceptability of the placebo.

Recent research suggests it might be possible to create a convincing placebo for a single crude herb.¹⁴ Progressive solvent extractions of *Artemisia afra* leaves removed most of the phytochemical constituents and left a relatively inert product that was made to resemble the

unprocessed herb in form, odor and taste. However, the processing is expensive, involved and might miss potentially active phytochemicals that are below the limits of detection for the given assay. These challenges will be far greater with complex formulae comprised of multiple herbs.

These difficulties of providing a relatively inert, convincing placebo that reflects the real world practice of herbal medicine are formidable. One possible way forward has been developed for a feasibility study exploring the role of Chinese herbal medicine in the treatment of endometriosis.

In this study a group of strong tasting culinary herbs and foods such as chicory, lemon balm, and turnips was used as a placebo tea. These plants are readily available in dried form, do not have strong therapeutic activity, and are not used in the treatment of endometriosis. Cooked together they produce a strong tasting decoction of a similar appearance to an active herbal preparation. Both placebo and active teas are packed in identical opaque muslin bags, cooked (unopened), and the resultant decoction is sealed into plastic sachets.

These food/herbs are not pharmacologically inert. However, absolute pharmacological inertia may not be possible. This approach, however, reflects real world herbal practice and is based on the assumption that individuated formulae of disease specific medicinal herbs should be able to demonstrate a greater therapeutic activity than what is effectively a mixture of vegetables. In addition, this approach allows clinically authentic, individuated herbal formulae to be compared with a relatively inert placebo. If successful it offers an affordable and accessible way to further the evaluation of decoction based herbal therapies. Approaches which can do the same for other forms of herbal intervention, particularly the use of tinctures, need to be developed and tested.

Researching the Herb as a Living Entity

Preliminary qualitative research among Western herbalists and herbalists who combine Western and non-Western herbal traditions suggests that “the herb” is identified by many, particularly those with a traditional orientation, as a “living entity.” This characteristic of the plant represents one key way that herbal whole systems are unique from other whole systems of healing. Specifically, it raises a set of research questions about the role and significance of this additional entity that participates in the healing relationship and process.

First, research is needed to further explore the nature of the plant, as perceived by herbalists and their clients. For many herbalists, the plant represents far more than an entity comprised of pharmacologically active constituents. Indeed, there exists the notion that plants have particular “essences” or contain energetic qualities that are not reducible to pharmacological activity. Some herbalists even express that plants have “spirits” or are “sentient.” Thus, the plant is perceived as having agency in the healing relationship and process that cannot be harnessed by reductionist means.

Second, the three-fold relationship between the herbalist, the client and the plant requires further articulation if we are to better understand the healing process and goals. Some herbalists, for example, regard themselves as facilitators of a relationship between clients and plants, and many articulate the goal of this relationship as the fostering of a “connectedness to nature”. Herbalists also often emphasize the importance of their own engagement with plants using the following terms: “sensitivity”, “appreciation”, “communication”, “intention” and “affinity.” Using similar language, Dennis describes the centrality of a “connection” in her study of herbalist-patient relationships that is: “based on helping intentions, mutual trust and respect.”¹⁵

Third, a deeper understanding is needed of how the perceived nature of the plant and the three-fold relationship shape treatment protocols as well as behaviors. Elliotson,¹⁶ for example, recounts that one herbalist's "connectedness" to a particular plant is one variable that influences a treatment decision. More broadly, herbalists emphasize the importance of a local connection to plants. For some, local plants are considered more "synergistic" to their clients than those grown in different regions or ecosystems. Furthermore, those herbs that are most likely to be needed by a client at a given point in time are believed to be found in that client's immediate vicinity. In some cases, clients are encouraged to gather and prepare their own medicines in an effort to foster connectivity to nature. In other cases, the practitioners take great care themselves in preparing their medicines with the appropriate and benevolent intentions that are believed to further contribute to the healing process.

The starting place for articulating these characteristics of herbal whole systems is exploratory, qualitative research that might include participant observation and ethnographic methods, in-depth interviews and/or focus groups with herbalists and their clients. Conducting such research across cultures, geographic regions and healthcare systems would be important to clarify variations that may exist with respect to this 'living entity' concept, and whether and to what degree it is present at all in any given context.

Designing Efficient Trials to Develop Herbal Whole System Therapies

Herbal whole system therapies are multi-component or complex interventions in that they often involve multiple herbs, along with other treatments like exercise, diet, and supplements. An important research question regarding such multi-component interventions is how to estimate the effect of a single component (e.g., a component herb or diet), or the interaction (e.g., positive or negative synergy) between two or more components present in an intervention. Once these quantities are estimated, one can eliminate components that are either inactive or that produce a negative synergy, and thus can potentially reduce cost and increase efficacy. One can also explore further to find the best dosage of components or the impact of additional treatments that have a positive synergy to increase the overall efficacy of the intervention.

As has been recognized in the literature,¹⁷ a "gold standard" RCT of a multi-component intervention versus a control does not directly address the questions of the action and safety of individual components (e.g., the herbal formula in the intervention versus the whole intervention such as diet exercise, herbal and supplement) and their interactions. Further, results based on any post-hoc secondary analysis that try to get at questions of interactions and/or isolated effects of individual components (e.g., one herb in a herbal formula versus the whole herbal formula) are generally biased and hard to replicate in the future, due to lack of randomization.¹⁷ In order to assay multi-component interventions The Medical Research Council of the UK¹⁸ provided a conceptual outline of a phased experimental approach for development and evaluation of multi-component interventions that includes several phases of empirical research and discovery leading up to and informing an RCT. Collins et al.¹⁹ provided a novel statistical approach called the Multi-phase Optimization Strategy (MOST), consistent with the above conceptual framework, to answer the questions regarding main effects and interactions of individual components of a multi-component intervention.

The MOST procedure embeds the standard RCT in a larger framework and consists of three ordered phases of randomized experiments, namely, screening, refining, and confirming. The screening phase aims to identify the active components of the intervention rather than finding their optimal dose. This is done by conducting a randomized experiment designed to obtain estimates of the effects of individual components and their interactions. The resulting experimental evidence provides the basis for preliminary decisions about which components to include in the multi-component intervention. Active components identified in the screening phase (usually fewer in number than the original set of components) are examined more

elaborately in the refining phase to find the best dosage. These two evidentiary phases precede and inform the confirming phase, which is a standard RCT to evaluate the multi-component intervention developed based on the results of screening and refining phases against appropriate control or placebo.

The MOST framework employs sophisticated factorial²⁰ designs that can simultaneously study several components (instead of studying one component at a time in an RCT) and hence serve the purpose of investigating individual components efficiently. In this factorial design, even though many components are studied simultaneously, the sample size and hence statistical power to detect the main effect of each component remains the same as testing that component in a two-arm RCT. Thus sample size requirement remains manageable. Moreover, this is the only class of designs that allows estimation of interaction effects. A technical discussion on MOST in general and factorial designs in particular is beyond the scope and aim of this article. Interested readers are referred to Nair et al.²¹ for substantial details on these topics.

MOST is a good methodology for development and evaluation of multi-component interventions for the following reasons: (1) strategic use of resources via efficient factorial designs, (2) sole dependence on randomized experiments rather than any post-hoc analysis, and (3) use of a confirmatory RCT only when an optimized intervention is reached (through the screening and refining phases). MOST has been successfully implemented in two large cancer prevention trials for developing optimal multi-component behavioral interventions.^{21,22} Based on the success of these trials, we sincerely feel that MOST has considerable promise for application in HWSR as well. With this novel approach, it seems possible to open the “black box” of herbal whole system therapies in a resource-effective manner. Careful research is needed in this direction.

DISCUSSION

The study of herbalism as a whole system of care has many of the same research issues faced when investigating other whole systems of medicine. Many of these challenges were elegantly reported in a paper by Ritenbaugh and colleagues.²³ These research problems encompass the development of analytical methods to study intact whole systems, looking at the complex interactions of patients and practitioners, attention to the environment where healthcare is provided, operationalizing and developing measurements for CAM whole systems diagnoses and treatment and the choice and development of appropriate study outcomes.

In addition to the methodological challenges listed above, herbalism offers its own distinct research difficulties. Some of these research challenges presented here, such as industry involvement, overlap with other aspects of whole systems research, such as the use of dietary supplements. However, herbals add additional levels of complexity beyond other non-herbal supplements. Non-herbal supplements generally are pure compounds such as quercetin or glucosamine that, despite different source material and manufacturing techniques, do offer a uniform and testable end product. Herbs in contrast, offer a blend of numerous compounds. To make things more complicated the practice of compounding different herbs in one formula presents almost intractable situations for analytical chemists and pharmacologists. Herbal extracts, even when manufactured in an identical manner, will have individual variations between batches. Consequently, manufacture of an herbal extract for research purposes requires careful in-process quality control and innovative technologies on the part of herbal manufacturers compared to the making of non-herbal supplements to make as consistent a product as possible.

Every whole system of medicine or healthcare needs to be defined for meaningful studies to be carried out on it. Herbalism is not singular in that it needs defining but in the unique aspects

of how researchers should go about defining it. In particular, herbalism is more often than not a part within a larger system such as Ayurvedic or Anthroposophic medicine, as compared to a system on its own. Thus, herbalism within larger systems such as Traditional Chinese Medicine should not be looked at separately from the overarching healthcare system. While homeopathy and certain manual therapies can make the same claim, of being entangled within other systems of healthcare, we would argue that herbalism represents the extreme of this situation and thus, offers a model for looking at and defining less entangled modalities such as homeopathy and massage.

Developing adequate placebos or controls is certainly not a new issue to complementary medicine researchers. Once again it is the distinctive needs of herbalism that make this a unique challenge. In particular, herbs are mainly administered orally. The norm is for randomized placebo controlled studies to reformulate these herbal remedies so as to be placed in capsules. The act of making an olfactory-rich and often liquid herbal extraction into an inert encapsulated product could diminish its therapeutic effects. Also, the action of making the extract by either the patient or the practitioner that could offer a significant part of the therapeutic action of the plant is removed. Moreover, the extra fluid ingested by the patient/client, the smells and taste of the extractions may all be methods through which an herbal treatment has efficacy. Consequently, keeping the original context of how the herb is delivered is extremely important and illustrates the difficulties of finding appropriate controls. This is in contrast with most other oral therapies such as nutritional supplements and homeopathic remedies that are generally given originally in a pellet or capsule format.

To address the methodological challenges of HWSR we suggest the following ideas as a starting place. It is important to develop a clear *a priori* definition of herbalists and herbalism tailored to the geographic location and practice standards of the study as well as its research goals. This should include clear distinction and definition of the difference between a lay and professional herbalists. We would also recommend that the use of herbal products only be considered as part of an herbal system of care when given, made or prescribed by an herbalist.

We would also encourage the development of novel partnerships being built between herbal manufacturers and herbal researchers from the earliest stages of the research process. These partnerships need to emphasize high-quality, transparent manufacturing processes with the willingness for all stakeholders to be aware of and participate in the areas of regulatory requirement. New marketing strategies and markets aimed at minimizing costs to both researcher and manufacturer need to be investigated in order to produce numerous research grade herbal products.

We propose the use of control, sham or placebo treatments that mimic how actual herbal remedies are delivered in “real world” practice environments. This means pursuing innovative methods and technologies for creating placebo liquid extracts such as teas and tinctures for both active treatments and controls. Once again this implies a close association with herbal companies at an early stage of the research process.

Another significant herbal whole system consideration is the importance of design and theoretical issues that would aid in capturing the perceived nature of the plant, and to the relationships between the plant, herbalist, client and “nature.” The starting place for asking these questions is exploratory, qualitative research that might include participant observation and ethnography, in-depth interviews and/or focus groups with herbalists and their clients. Such research at the developmental phase of a HWSR design would help to inform the identification of key assumptions, norms, concepts, processes, and theories, including practitioner and client perspectives; the choice of meaningful and appropriate outcome measures, e.g., “connectedness to a plant”; the framing of key concepts/theories/assumptions

in terms of testable hypotheses, e.g., the more “connected” an herbalist is to a plant and to the client, the greater the chance of a successful intervention; and the development of meaningful qualitative research *questions* directed at herbalists and clients.

Health outcomes research is another manner in which to address HWSR. Examining visits to an herbalist versus, for example, standard of care is a promising method for examining herbal systems of medicine as complete multi-component packages of healthcare. Health services researchers could incorporate qualitative assessments that probe the relationships between the plant, herbalist, client and “nature”, as described above. In addition, a careful definition of an herbalist and an herbal system should be applied to health services research to ensure that “the system” being studied is consistent with the researchers’ goals and to decrease heterogeneity in the system.

Lastly, we recommend the use of novel statistical methods as innovative solutions to HWSR questions. One such example of a novel statistical design is the MOST method. This method allows researchers to examine the main effects as well as synergistic effects of herbals within the context of a complete treatment regime. Moreover, the MOST method could be used to create more efficacious and cost-effective herbal treatments.

An area of herbal research that, while important, is outside the scope of this paper is finding the proper dose of an herbal or herbal formula either outside of or within the context of a whole herbal system. Finding the proper dose is a methodological problem that will require a variety of expertise from pharmacologists to biostatisticians to qualitative researchers. Consequently, identifying an herbal dose to use in a study and optimizing that dose deserves a paper of its own to address this topic.

In summary, HWSR presents novel methodological challenges that encompass but extend beyond those presented for whole system research in general. The unique challenges of HWSR offer considerable barriers to conducting research in this area, however, innovative solutions are possible. These solutions include developing close relationships with herbal companies, developing appropriate herbal products and placebos, using new statistical techniques to explore synergistic and individualized effects of treatment, and in-depth qualitative exploration into the nature of “the plant” in an herbalist-client interaction. Use of these solutions offers a starting point for conducting successful HWSR.

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