Facilitating IRB Consideration of Protocols Involving Complementary and Alternative Medical Therapies

This article reviews the application of institutional review board (IRB) rules to clinical research involving complementary and alternative medicine (CAM). Such research raises several challenges, including: the evaluation of the risks and benefits of CAM studies given a lack of familiarity with this area and a lack of sufficient scientific information regarding the safety and efficacy of these therapies; difficulties in gaining IRB approval of CAM practitioners as coinvestigators; and difficulties in meeting IRB-mandated protocol requirements. This article provides policy recommendations to facilitate IRB consideration of proposed CAM studies. (*Clinical Researcher* 2004;4(3):12–6.)

As a result of inadequate oversight by academic medical centers and other institutions, there has been greatly increased federal supervision and judicial criticism of research involving human subjects. Key developments include the development of a federal Office for Human Research Protections (OHRP), and recent action against several universities for the violation of research rules to protect human subjects. Notable cases have included actions against the Fred Hutchinson Cancer Research Center, WA, USA, the University of Pennsylvania, PA, USA, and Johns Hopkins University, MD, USA [1–4]. In a recent court case, involving a university, the investigators' research protocol was strongly criticized, along with the informed consent process, and the institution's review and approval process [5].

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Despite such increased supervision, studies of CAM therapies (eg, chiropractic, acupuncture, traditional oriental medicine, and massage therapy) have not received significant attention from the regulatory authorities involved in human subjects research. This article reviews the regulation of clinical research in the USA and offers analysis and policy suggestions regarding the application of IRB rules to research involving CAM therapies.

US clinical research regulation – a brief history

Federal regulation of clinical research conduct has evolved through a series of regulations designed to protect individuals participating in medical experimentation. Following the 1946 Nuremberg trial of Nazi war criminals, the "Nuremberg Code" established a set of principles to govern

the ethical conduct of research. The key principles are that [6]:

- the voluntary consent of the subject must be obtained
- prior animal experimentation to determine risk must be performed
- human experimentation must be performed by qualified medical personnel

These rules evolved further through iterations such as the World Medical Association's "Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects" [7]. Further revelations of continuing ethical violations in the medical literature – including reported failures to provide informed consent and to treat human subjects who had syphilis in the Tuskegee Syphilis Study [8] – led in 1974 to the passage of the US National Research Act, which established a commission to define ethical standards for research and required the review of all clinical research by an IRB [9].

By 1975, the commission's recommendations were published as the "Belmont Report", which established key principles for assessing whether a program of clinical research is ethical [10]. These key principles are:

- autonomy (including obtaining informed consent, protecting privacy, and maintaining confidentiality)
- beneficence (including assessment and disclosure of risks and benefits to the patient)
- justice (including equitable selection of subjects)

Following the "Belmont Report", the federal government formalized the "Federal Policy for the Protection of Human Subjects" (also known as the "Common Rule"), to operate across federal agencies and departments. This rule requires informed consent and IRB review for all federally funded research studies [11].

In 2000, the US National Institutes of Health (NIH) began to require all investigators submitting NIH grant applications or receiving new or competing research awards to be educated on the protection of human subjects [12]. Today, regulations promulgated by the US Department of Health and Human Services (HHS) are administered by the OHRP and apply to any research funded by the HHS (including NIH sponsored research) [13]. In addition, US Food and Drug Administration (FDA) regulations apply to any research that involves FDA-regulated products.

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The IRB review process

The IRB must evaluate and decide whether to approve proposed research based on whether the following criteria are fulfilled [14,15]:

- risks to subjects "are minimized"
- risks to subjects are "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result"
- selection of subjects is "equitable"
- informed consent is sought from each prospective subject or the subject's legally authorized representative
- informed consent is "appropriately documented"
- the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (where appropriate)
- there are "adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data" (where appropriate)

In addition, when subjects "are likely to be vulnerable to coercion or undue influence" (eg, children, prisoners, pregnant women, and handicapped, mentally disabled, economically disadvantaged, or educationally disadvantaged persons) "additional safeguards… [must be] included in the study to protect the rights and welfare" of these subjects [14,15].

IRBs also require investigators to provide research subjects with the basic elements of informed consent mandated by federal regulations [16], including:

- a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's

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participation, a description of the procedures to be followed, and the identification of any procedures that are experimental
- a description of any reasonably foreseeable risks or discomforts to the subject
- a description of any benefits to the subject, or to others, that may reasonably be expected to result from the research
- the disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- a statement describing the extent to which confidentiality of any records identifying the subject will be maintained and, where an FDA-regulated product is being used, noting the possibility that the FDA may inspect the records

Academic medical centers may have multiple IRBs, including IRBs affiliated to local hospitals as well as a central IRB for the host institution. Within an academic medical center, each IRB will have a continuing review subcommittee that approves, rejects, or defers research on an ongoing basis. The definition of "human subject" generally means a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual, or through identifiable private information. Consequently, in academic medical centers IRB approval is required not only for research involving patients but also for research with tissue or data that is linkable to an individual. Therefore, IRB approval is also required for federally funded research in the areas of public health, psychology, sociology, history, education, communication, and even internal institutional quality assurance.

Table 1. Challenges to institutional review board approval of complementary and alternative medicine (CAM) studies.

- Lack of familiarity with CAM therapies
- Making an accurate risk–benefit analysis
- Approving the CAM coinvestigator
- Meeting protocol requirements
- Determining doses and gaining hospital approval for dietary supplements

IRB issues specific to research involving CAM therapies

There are several obstacles to IRB approval of even rigorously designed CAM studies (see Table 1). First, although regulations specify the minimum composition of IRB membership (five members "with varying backgrounds" and "diversity… including consideration of race, gender, cultural backgrounds and sensitivity to such issues as community attitudes" [17]), the regulations do not require that any of the members have experience of CAM research or clinical practice. Indeed, until experience of CAM research and clinical practice becomes more widespread in US hospitals and academic medical centers, IRB members are likely to remain inexperienced in this area. Even if investigators apply the same standards to the study of CAM therapies as to the study of conventional therapies, innovative study designs may be required as some forms of CAM research involve distinct methodological challenges. In many cases, the mechanism of action of the CAM therapy may be unknown (eg, the use of moxibustion to correct a breech presentation in childbirth) and study designs may include only selected elements (eg, a designated acupuncture point) of a whole medical system foreign to biomedicine (eg, yin–yang and meridian theory in traditional oriental medicine). Even if a recognized study technique is used (eg, sham needles in the testing of acupuncture efficacy), the lack of general medical acceptance for the modality or philosophy behind the modality's claims of efficacy may complicate the IRB's evaluation.

Second, IRB criteria for approval include the requirement that the risk to the subject is minimized and is reasonable in relation to the anticipated benefits (if any), and the importance of the knowledge that is expected to result. However, the risks of many CAM therapies have not been well-studied in animal populations, let alone in human subjects (eg, the use of homeopathy and/or chiropractic to treat ear infections, and the use of herbal medicine more generally). Therefore, potential risks, as well as benefits, may be difficult to measure or report.

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Third, it may be difficult to approve CAM practitioners as coinvestigators on a research team. To minimize risks to human subjects, the IRB may wish such coinvestigators to have medical oversight when rendering an intervention (eg, during spinal manipulation or acupuncture needling), but the requirement for such oversight may conflict with independence given to the provider by the relevant state's licensing laws [18].

Fourth, it may be difficult for studies of CAM therapies to meet some IRB-mandated protocol requirements (eg, it may be difficult to find controls for some CAM practices at the borderland of medicine and religion, such as the Native American sweat lodge). Similarly, when IRBs call for a description of the observations and measurements to be made to fulfill IRB-mandated protocol requirements, the kinds of observations made by CAM practitioners (eg, the intimate readings given by pulse diagnosis in traditional oriental medicine) may be different from observational techniques assumed by Western scientific methods.

Finally, because the Dietary Supplements Health Education Act of 1994 allows dietary supplements to be manufactured without prior proof of safety or efficacy, there are many supplements for which accurate and consistent doses are not generally available. Therefore, it may be difficult to assign a method for determining dosage, planned maximum dosage, and duration of patient exposure. Similarly, while IRBs often require a description of clinical procedures, lab tests, or other measures to be taken to monitor the effects of the drug and to minimize risks, a reliable evaluation of serum levels may be unavailable for dietary supplements. Likewise, it may be difficult to perform protocols involving

herbs if these substances have not been approved for use in the relevant hospital. To date, scientific literature to validate safety and efficacy has been lacking for many dietary supplements, and it is likely that literature from CAM providers regarding the purported benefits of specific supplements would be discounted.

Policy recommendations

As already suggested, at present, many IRBs lack the expertise (or familiarity) to adequately evaluate studies involving CAM therapies originating in non-Western medical systems. Researchers may find it difficult to sufficiently evaluate and articulate risks and benefits, to get CAM coinvestigators approved, and to meet protocol requirements. The lack of sufficient scientific information regarding the safety and efficacy of dietary supplements may complicate efforts towards adequate scientific investigation. However, the greater the numbers of well-constructed proposals to investigate CAM therapies that are approved, the sooner that clear scientific information will be available to consumers. This will help to resolve some of the ideological and methodological murk surrounding these therapies, which are widely available and delivered by a host of licensed CAM providers [18]. Our recommendations in response to these challenges are included below (see also Table 2).

First, the inclusion of appropriate experts on the IRB who are familiar with the CAM therapy to be studied (eg, a licensed chiropractor, massage therapist, or mind–body provider who understands standards of care and the appropriate professional expectations for any given intervention) would facilitate appropriate IRB review of such proposals.

Second, when evaluating a proposed study's risks and benefits, the IRB also should take into consideration data regarding consumer usage, usage within the medical community, and any use or approval of the CAM modality by government agencies (eg, chiropractic manipulation has been accepted as a treatment for acute lower-back pain by the US Agency for Health Care Research Quality [19]).

It may be difficult to perform protocols involving herbs if these substances have not been approved for use in the relevant hospital

Third, when assessing risks and benefits, IRBs should look to frameworks used by clinicians to assess malpractice liability risk, and should consider the ethical issues surrounding the use or avoidance of CAM therapies [20,21]. As such frameworks use the clinician's perspective, and they can provide parallel viewpoints to the IRB's risk–benefit analysis, they may offer useful models for assessing the decision to offer (or not offer) CAM therapies to patients when the kind of data generally available for many conventional therapies is absent.

Fourth, when assessing protocols and qualifications in investigations involving CAM practitioners, IRBs may wish to consider the way applicable rules for licensure, credentialing, and scope of practice for CAM providers structure CAM-provider authority and practice [18,22], since such rules also shape the clinical delivery of CAM care and the integration of CAM therapies into conventional medical settings. For example, such rules may or may not require physician referral prior to patient treatment, delimit the modalities the provider is allowed to use, or delineate supervision requirements.

When assessing risks and benefits, IRBs should look to frameworks used by clinicians to assess malpractice liability risk and consider ethical issues

Finally, when evaluating proposals involving dietary supplements, IRBs should consider the extent to which consumers are already using (and licensed CAM providers recommending) the supplements proposed to be studied, since such extensive use would suggest that further study is critical to enhancing available information concerning safety and efficacy.

Conclusion

The situation relating to IRB consideration of studies involving CAM therapies is continually evolving. Over time, with implementation of the above policy recommendations and the increase in scientific knowledge and IRB familiarity with CAM clinical practice and research, investigators may find greater opportunities for scientific progress in this arena.

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Table 2. Challenges and policy recommendations for complementary and alternative medicine (CAM) studies.

Challenge	Policy recommendation
Lack of familiarity with CAM therapies	Include CAM experts on the institutional review board
Making an accurate risk–benefit analysis	Include data regarding consumer, medical, and government usage Look to CAM malpractice assessment and ethics frameworks
Approving the CAM coinvestigator	Understand and review CAM practitioner licensure, credentialing, and scope of practice
Meeting protocol requirements	Understand and review CAM practitioner licensure, credentialing, and scope of practice
Determining doses and gaining hospital approval for dietary supplements	Examine existing consumer usage

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