GENERAL RECORD INFORMATION

Request Identifier: 12242885
Request Date: 20050914
OCLC Number: 30084937
Borrower: BTS
Receive Date: 
Due Date: 
Lenders: *UNB, BZI, ELW

BIBLIOGRAPHIC INFORMATION

Call Number: Lender's Holdings: v.5- 1999-
Uniform Title: Journal of alternative and complementary medicine (New York, N.Y.)
    Title: The journal of alternative and complementary medicine: research on paradigm, practice, and policy.
    ISSN: 1075-5535
    Imprint: New York, NY : Mary Ann Liebert, c1995-
    Article: Harlan WR 'New opportunities and proven approaches in complementary and alternative medicine research at the National Institutes of Health'
    Volume: 7
    Number: Suppl 1
    Date: 2001
    Pages: S53-S59
    Verified: <TN:59644> OCLC

BORROWING INFORMATION

Patron: Sommer, Rebecca
Ship To: ILL/BATES COLLEGE LIBRARY/48 CAMPUS AVE/LEWISTON, ME 04240
Bill To: Same; FEIN 010-211-781-51; CISTI acct:DD727411; BRI acct:51-9034; UMI acct:B98001
Ship Via: ariel/fax
Maximum Cost: IFM - $20
Copyright Compliance: ccg
    Fax: Ariel 134.181.176.73 FAX: 207-786-6055
    Email: ill@bates.edu
Affiliation: NELINET/OBEGROUP/LVIS
Borrowing Notes: @N, BOS/PAU coupon

LENDING INFORMATION

Lending Charges: 
Shipped: 
Ship Insurance: 
Lending Notes: 
Lending Restrictions:
New Opportunities and Proven Approaches in Complementary and Alternative Medicine Research at the National Institutes of Health

WILLIAM R. HARLAN, Jr., M.D.

ABSTRACT

This presentation describes some of the issues that arise when applying the clinical-trial approach of conventional medicine to complementary and alternative medicine (CAM) modalities. Conventional medicine has been making the evolution to using an evidence base and to making recommendations only when the evidence is strong. The National Center for Complementary Medicine (NCCAM), one of twenty-five Institutes or Centers of the National Institutes of Health (NIH), is working to hold CAM to the same high standards, not by rejecting previous CAM research, but by building on that strong evidence base of what works and what is safe.

The process for conventional drug and device development follows an orderly process of preclinical studies (usually on animals), phase I, phase II, and phase III studies (with the large human clinical trial phase taking place in phase III). Today, the randomized controlled trial is recognized as providing the highest level of scientific evidence. This conventional medicine approach to development is now being used to develop complementary and alternative therapies. For instance, the discovery and development of Taxol (Bristol-Meyers Squibb, New York, NY), an extract from the bark of the Pacific yew tree that is now a widely used chemotherapeutic agent, followed the conventional pathway to approval and marketing. But for most CAM products, the pathway is not so straightforward. Most CAM therapies are traditional therapies or new products that are already available to the public. Most of what is known about these therapies is of an anecdotal nature. There has been little isolation of the active principals from the crude product and there has usually been no preclinical testing.

This presentation details various approaches and programs that address how to plan and conduct a rigorous clinical trial of a CAM product. And, while it takes a good deal of persistence and a strong focus on what are the critical principals in a trial, I conclude that it is possible to apply randomized controlled trials to most of the CAM modalities.

This presentation focuses on the issues of developing the evidence base for complementary and alternative medicine (CAM) through clinical trials. There are issues in developing clinical trials that are unique or different. My presentation is based on personal experiences in planning and conducting clinical trials in conventional medicine and subsequently in the development of the clinical trial portfolio that exists now in the National Cen-

Public Health Service, National Institutes of Health (NIH), Bethesda, MD. At the time of the meeting, Dr. Harlan was Acting Director of the National Center for Complementary and Alternative Medicine at the NIH.
Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH).

The goal is the creation of a scientific base for prevention and management and to provide recommendations to the public and health providers. The randomized controlled trial provides the highest level of evidence (Fig. 1). Medicine and public health have been making this evolution to using an evidence base and making recommendations only when the evidence is strong. CAM is not being held to a higher standard. In fact, it is being held to the same standard. So it is not that we don't believe all that went before. It is not that we don't think that good research has not been conducted. It is that we want to build that strong evidence base about what works and what is safe.

The initiation of planning for a clinical trial is the compilation of information about what therapies are currently being used and what are the observations about their value and their side-effects. The surveys that Dr. Eisenberg has done have added greatly to our knowledge. We are conducting another survey of a slightly different type on cancer. In that set of studies, we have the cancer centers that have population-based registries of all cancer patients within particular areas. We are surveying now for the use of CAM modalities, along with the use of the conventional modality. It is a population-based, surveillance study—so that the individuals will be followed and we will have an opportunity to see whether there is a difference in side-effects; whether there is a difference in outcome with the use of complementary and alternative therapy.

The NCCAM is conducting practice evaluations along with these surveys. This is done by examining a best-case series—or the experiences of practitioners with the treatment of cancer using CAM modalities. The information from surveys, best-case series, structured reviews, and observational studies are evaluated to determine whether this approach is promising and worthy of further study. This can lead to a large, randomized controlled trial to provide a definitive test of efficacy.

When one looks at all of the therapies being used, there are an extraordinary number. There are too many opportunities and there is too little time and too little money. Much of this process is dedicated to trying to pick out the most promising opportunities and to make this much larger investment in the randomized controlled trial. Characteristic of these is large sample size. The randomized controlled trials are, as you might expect, very expensive. The costs range anywhere from 3 million U.S. dollars to as much as 50 million U.S. dollars over the course of the study. Before making this large investment, one would want to have the kind of antecedent information that allows one to make an estimate of the clinical value, of the power of the trial to answer the question, and of the likelihood that a trial can be successfully and ethically conducted.

The process for conventional drug and device development follows an orderly process; and this has been used by pharmaceutical firms and device manufacturers. Active drugs are screened through preclinical studies. Such drugs may have been created through synthesis based on molecular understanding of the alteration caused by disease. Considerable information about the physiology, the pharmacology, the activity, the mechanisms of action and, to some degree, the toxic side-effects are compiled from doing this preclinical work. This occurs primarily in animals. Phase I studies are the first human studies done in a small number of individuals to determine that an agent is active and not overly toxic. Then there is phase II, during which individuals with a

---

**Evidence-Based Medicine and Public Health**

- Decisions about an approach to prevention and treatment should be based on proof of efficacy and comparisons of treatment benefits/risks between new approach and usual care approach
- What constitutes the evidence base?
- Should time-tested (but not trial-tested) approaches be grandfathered or subject to the same testing as new conventional approaches?

FIG. 1.
particular condition or disease are studied in larger numbers and biomarkers and other indicators of activity against disease are assessed. Finally, the treatment is studied in phase III, a large clinical trial.

This kind of orderly or conventional drug and device development is also being used for complementary and alternative therapy. The National Cancer Institute has a program to screen natural products and test them. Taxol (Bristol-Meyers Squibb, New York NY), from the bark of the Pacific yew tree, is an example of the success of this program. Taxol is now the most widely used chemotherapeutic agent for cancer and resulted from the orderly development of natural product screening.

The discovery and development of Taxol followed a conventional pathway to approval and marketing. But most CAM products have a considerably different course (Fig. 2). Most therapies are traditional therapies or new natural products that are freely available to the public without testing or licensure. Most of what we know about them comes from reports of anecdotal experience—case reports, often historical reports, and sometimes small observational studies. There is usually no preclinical testing. There is little isolation of active principals from the crude product. Characterization of the material is inadequate. Adverse effects and toxic effects are incompletely characterized. That information is needed for large-scale studies.

To remedy this lack of information, the NIH has recently developed a botanical centers program (Fig. 2, lower right corner). This is a joint program between the Office of Dietary Supplements and the NCCAM. It is dedicated to carrying out the phase I/phase II-type studies for many of the therapies that have a great deal of promise and that, in fact, may be just about to enter large clinical trial testing. The Centers will characterize and standardize the material—its consistency over time—and, in some instances, will try to purify the active principals.

One other source of information has been the smaller trials that have been conducted, some within the NCCAM Centers that I noted previously. And the information there sometimes provides both phase I and phase II information. The process of CAM development can follow the conventional pathway of efficacy and safety testing, but additional mechanisms are needed to provide crucial information for phase III studies.

The conduct of large, randomized controlled trials is important to the public and pharmaceutical firms that cannot gain exclusive financial control and are unlikely to pay for it. The public sector will support most trials in the interest of the public. What are the necessary aspects of a trial? Trials are conducted to provide an unbiased assessment of the efficacy of an agent or procedure. The characteristics of an effective trial are given in Figure 3. Randomization assigns eligible participants to be placed on a specified regimen. The assignment must be truly random, and preferable assignment status should be masked to the participant and investigator. This makes it unlikely that treatment will be preferentially given to one group.
based on its desire for a specific treatment or prerrandomization health status or characteristics. The randomized groups are similar before the study starts and the outcomes can be attributed to the treatment, not the prestudy status of the groups.

A placebo is often necessary in the control group. A significant proportion of individuals (often 10–40%) will respond to an inert pill or sham procedure. This is an especially important consideration when the outcomes are subjective, such as pain or nausea, and the investigator is dependent on the participant’s report to determine efficacy. This is an important issue in CAM studies. There is no question that people respond to a placebo. And in fact, its very name, “I shall please,” suggests that they should respond. The response varies across cultures and is quite different in different parts of the world. The response varies directly with the enthusiasm of the investigator—the person who applies the therapy. This placebo response will apparently differ in different conditions. A placebo control, when it can be carried out, is extraordinarily important.

We believe a comparative agent, when there is a conventional therapy that is customarily used, is important. It is useful in terms of putting the CAM modality into perspective. We seldom power the trial, however, to be able to find a difference between the CAM modality and the conventional comparative agent. This would require a very large trial because often the expected difference is quite small, requiring a large sample size to estimate the difference. The comparative agent can permit a comparison with a placebo control and the CAM therapy will be compared to the placebo. The specification of the expected difference is important in powering the trial and estimating the required sample size.

Many CAM studies focus on relief of subjective symptoms and improvement of general well-being and these generally are used to measure outcome. Most of the clinical trials in conventional medicine use mortality or other objective clinical measures as endpoints. And, in CAM, many of the treatment modalities have subjective outcomes assessment. If a subjective assessment is to be used, it needs to be clearly structured so that the difference between the intervention and the placebo is clearly delineated. Again, the theme is discovering what works.”

The NCCAM has several large clinical trials underway, and these studies illustrate some issues that arise developing and conducting clinical trials in CAM (Fig. 3). This study compares St. John’s wort (Hypericum perforatum) and a selective serotonin receptor inhibitor to placebo in moderately severe depression. The patients are screened for moderately severe depression and one of the three treatments is randomly assigned. The St. John’s wort and depression study examines a more severe degree of depression than other studies. A standardized scale is used to assess the degree of depression and the changes in each group with assigned treatment.

A study of Gingko biloba to prevent cognitive decline in older individuals is underway and uses a placebo control. An elderly population was selected because we know that they will be moving through a period of cognitive decline at about the rate of 2–4% per year. The intent of the study is to lessen the predicted decline. The required sample size is large (several thousand men and women). The measure of cognition is structured and includes a standard questionnaire and interview, as well as assessment of social functioning. The changes over the several years of follow-up are likely to be small and somewhat variable, so the study population must be relatively large to provide a confident measurement of differences.

A systematic review of smaller clinical trials can provide a realistic estimate of the expected size of effect. In St. John’s wort, for example, many smaller, randomized and nonrandomized studies described a reduction in the depression scale that was in the range of 50%. And yet, when all randomized studies were combined in a meta-analysis, the estimated effect was 20–30%. This more realistic effect size led us to use a larger sample size and one that would test for the lesser effect with statistical confidence.

An important consideration in these studies of herbal products is the purity and uniformity of the material. Many products containing St. John’s wort are commercially available in the United States. However, the amount of Hyper-
cum that is present in the preparation varies from 10% of the stated amount to 120% of the stated amount. This problem of standardization and uniformity of material presents a problem in the conduct of a clinical trial and also in obtaining consistent effects in clinical use. There is another problem. The bioavailability and interactions with other herbals or conventional drugs are unclear.

The development of botanical centers should provide information on active principles and on interactions. But there is another aspect to this that one shouldn't forget. Manufacturers have, thus far, not been required to meet any manufacturing requirements and, therefore, the materials are not standardized. This should change with regulations on good manufacturing processes being promulgated by the Food and Drug Administration. The entry of the ethical pharmaceutical firms into the field will improve standardization. These issues remain very important in planning the trial.

In planning large "definitive" CAM trials, it is important to use realistic estimates of the effect that can be expected in the population to be studied and to include adequate numbers of persons to find a treatment difference from placebo or to find an absence of a useful effect. It is important to keep in mind that, within the placebo control, there will be a number of participants who respond with beneficial and adverse effects. An estimation of the placebo response can be helpful. Again, the use of smaller studies, where the placebo response has been determined, provides a reasonable estimate.

The trials sponsored by the NIH differ in duration from those usually sponsored by pharmaceutical firms, and this difference extends to CAM studies. Trials for the licensing of drugs in the United States usually are conducted over brief periods of about 16 weeks. On the other hand, many of the studied conditions (depression, hypertension, and others) do not last just 16 weeks. They are long-term chronic diseases. If we were to do a 16-week study, we might not capture those individuals that discontinue therapy before, or those whose conditions do not respond after this period.

These chronic conditions should be studied over longer periods, the long intervals over which treatment should be taken. This is true with CAM as well since many CAM preparations are proposed for long-term conditions. There is another important aspect: CAM modalities are touted as less toxic and more likely to be taken long-term by patients than conventional drugs. If this is true, then long-term comparisons would favor CAM as patients would discontinue conventional medications while continuing CAM. However, this should be put to the test. The trials of St. John's wort, *Gingko biloba*, and chondroitin sulfate/glucosamine are being tested over long periods for the management of depression, cognitive decline, and osteoarthritis, respectively. The lesser long-term side-effects and greater patient acceptance could prove a superiority of CAM therapies, even if the outcomes were equivalent to conventional medications.

The use of a placebo is important in CAM trials, both of medical preparations and physical approaches. Modalities that depend on physical contact—acupuncture, massage, chiropractic—pose a difficult problem with respect to development of placebo control. The placebo must be something that is plausible to the participant; perhaps a physical intervention, but not have known therapeutic activity. It has to be something that, it is hoped, will blind individuals as to whether they receive the active intervention or an inactive intervention. The expectation of receiving the intervention is very important. If they did not receive the treatment, but they had expectations, they might do worse than individuals who did not participate in the study and were just assessed. It is very difficult to mask physical interventions without carrying out a plausible sham. Acupuncture for relief of pain presents a classic example. Placement of needles in the skin may be considered a placebo if the placement is inappropriate to the classical site, or if placement is too superficial to achieve *de qi*, or if no physical stimulus, twisting, or electrical current is applied. In most instances, this "sham" placement produces symptomatic relief over no needle placement, but less improvement than the "active" acupuncture. The fact that there is improvement with the "sham" placement attests to the importance of a plausible placebo for physical CAM modalities.

An important methodological issue in CAM
trials is testing the treatments that are custom-designed for individuals based on particular individual characteristics. This is the basis for traditional medical systems that include individualized diagnosis and treatment based on observations and not on diagnostic categorizations. Can the systems of complex and tailored treatments be evaluated with a randomized controlled trial? This has been attempted in the Western conventional setting. Some studies have randomly assigned patients on admission to hospital to a particular service. There is no blinding of therapist or patients. However, the participants must be informed about the alternatives, and the therapist and trialist must believe that the alternative approaches are roughly equivalent. With this kind of study design, having an objective assessment of outcome is absolutely crucial. In evaluating complete systems of care, the study population might be randomized to separate therapeutic groups to receive a total systems approach. However, the participants must be willing to be randomized. The Gonzalez therapy for pancreatic cancer is a very complex therapy that requires tailoring by the therapist and some alterations in the therapy during the course of the therapy. It consists of a proteolytic enzyme plus a dietary-support approach. The outlook for pancreatic cancer is so bleak that patients self-refer in desperation. The initial studies have had no control groups, making it difficult to be sure that the observed improvement in survival was the result of the treatment. One difficulty is that patients who are attracted to this therapy are unwilling to be randomized not to receive it. This hinders recruitment and dropouts can increase. A parallel comparison of matched patients not receiving the Gonzalez regimen might be the only feasible approach.

These are some of the issues that are related to CAM trials, but there are many others that are common to conventional drug trials. For example, should the individual assessing outcomes be different from the trialist who is conducting the study? In large studies, this is not a problem because there is usually a separate evaluative team. But as you look at some of the tailored approaches, it becomes quite difficult to keep the individual therapist, who is the proponent of the therapy and is altering therapy, totally divorced from the follow-up of the patients. And obviously, when these therapies are individualized, the evaluator may not be blinded to the allocation to the therapeutic group. Complete blinding or masking is not possible, but the evaluator might be blinded.

While there are issues that arise in CAM about conducting randomized controlled trials, I think that most of them can be approached constructively. It takes a good deal of persistence and a strong focus on what are the critical principles in trials. It is possible, in most instances, to have randomized controlled trials applied to most of the CAM modalities. When this is not possible, full disclosure of methodologic approaches will alert the clinician about reservations concerning the conclusions.

These are issues that require individual attention. There is not a "one-size-fits-all" approach. There is not a general approach that can be applied to all of them. It will take considerable collaborative work between the CAM community and the conventional community—particularly the design experts. But that has been true, incidentally, throughout the relatively brief history of clinical trials. You should bring the people together with experience, the people with the design expertise, and have them work individually through these problems to develop a study that will give us a confident answer about efficacy and safety. The future is quite bright for randomized controlled trials in CAM therapy. Thank you.

(In reply to a question from the audience): I was asked the question: "In the CAM clinical trial, what size and number of controls in the green-tea group is optimum, and how long does it take to assess the green-tea effect?" Actually, they have not started the large clinical trial in green tea (Camellia sinensis). They only have been purifying the preparation. One could make some estimates based on what we understand the effect-size to be. But that would be dependent on the earlier studies that had been conducted—the preclinical studies—phase I/phase II studies. And part of this question is: "Could you tell me the optimal sample size, and the optimal duration for CAM assessment?" I think that what I’ve said is that this will vary with the effect that you expect to see with the intervention. And a good estimate
of effect size is absolutely crucial in determining the size of the study population. You have to take into consideration, obviously, dropouts and some other aspects that will mean people lost to the study. The optimal duration will depend on how long it takes to move to the effect that you are seeking. There is a lag between therapy and effect. There is a lag between the effect of the therapy and the change in some outcome parameters, such as tumor size, or even a change in symptoms. We want to be sure that we have an accurate estimate, so that we can have the trial long enough to detect the effect that we are seeking. As I have said earlier, I think it is probably very important that we conduct longer studies rather than shorter studies, because some of the advantages of CAM may come in this long-term effect, and the lesser toxic effects of the CAM therapy. This is particularly true when we are looking at chronic diseases and trying to make estimates of the value in chronic diseases. So these are all each individually determined and are dependent on the characteristics of the treatment, and the characteristics of the disorder that we are treating. Thank you.

Address correspondence to:
William R. Harlan, Jr., M.D.
National Institute of Mental Health
Neurosciences Center/DSIR
Room 7117
6001 Executive Boulevard
Bethesda, MD 20892-9629

E-mail: wharlan@mail.nih.gov