



**August 2008: Cancer Clinical Trials Series: Ethics and Safety
"Ethics in Clinical Research"
By Benjamin Marchello, MD, Principal Investigator, Montana
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Ethics must be considered for any experimental program. The Nuremberg Trials after World War Two and the sad tale of the Tuskegee experiments in this country have given a background for strict scrutiny of research. First the scientific basis of any trial must meet ethical standards. Second, informed consent must be obtained. Third, the analysis of the trial must be unbiased. Finally, there must be no conflict of interest for the researchers.

Of course the goal of cancer research is to improve the lives of the participants and other cancer patients, but to do so the scientific basis must be valid. Any new treatment must have rigorous analysis of the previous research suggesting new benefit. A comparison between treatments must have perceived balance between treatments for effectiveness and toxicity. The possible benefits must outweigh the risks of treatment, including physical, psychological, social, and economic effects. Before a trial is ever developed these factors must be considered.

Informed consent is the basic understanding between the researcher and the subject (the doctor and the patient.) Extensive planning occurs to make sure a subject understands risks and benefits. The language must be clear and the information complete. We have institutional review boards right here in Montana that approve our consents even though they have been developed by experts and reviewed at a national level. In the end a personal explanation and personal answers from the doctor to the patient is needed.

Once a trial is underway it still has to be reviewed. All persons must be allowed access to a new treatment with only scientific exclusions for the study, no social exclusions. The data must be honest and complete to give a useful answer. Mistakes and fabrications must be caught by reviews and audits. Any drastic unexpected results must be caught by a data monitoring committee to stop or change a study as needed. And the results of a study must be published quickly to get new information out to benefit cancer patients.

Finally conflicts of interest must be clear. The actual research results must be measured and analyzed by persons with no financial or professional stake in the results, or at least potential conflicts must be revealed to allow others to consider this with the results. The full study results must be openly available for other scientists to give impartial review and criticism.

When patients' lives depend on our research we need to get it right. We may not get perfection, but every step forward reduces suffering, extends lives, and gives us all hope.



**August 2008: Cancer Clinical Trials - Ethics and Safety
"IRB"
by Amanda R. Dinsdale, CCRC, Program Coordinator,
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What is an IRB?

An Institutional Review Board (IRB) is a committee that has been formally designated to review and monitor biomedical research involving human subjects. An IRB may also be referred to as an independent ethics committee (IEC) or an ethics review board (ERB). In accordance with Food and Drug Administration (FDA) regulations, an IRB has the authority to approve, require modifications (to secure approval), or disapprove clinical research. The role of the IRB is to protect the rights and welfare of human subjects in research.

History

Prior to the twentieth century, research ethics were primarily governed by individual conscience and professional codes of conduct. Whether and how humans might be protected had been subject to the laws and customs of the society and government at the time. IRB's were developed in the 1970s in direct response to research abuses earlier in the twentieth century. Two of the most notorious cases of abuse in history were the experiments of Nazi physicians that became a focus of the post-WWII Nuremberg Trials, and the Tuskegee Syphilis Study, an unethical project conducted by the US Public Health Service on poor, illiterate black men in rural Alabama. Originally, IRBs were local committees at hospitals and academic institutions. Today these local IRBs still exist but there are also independent or commercial IRBs. The responsibilities of these IRBs are the same and they are governed by the same federal regulations.

Composition

IRBs are governed by the FDA and the Department of Health and Human Services (DHHS), specifically the Office of Human Research Protections (OHRP). The composition of an IRB per FDA requirements is as follows:

- * An IRB must have at least five members
- * The members must include both men and women
- * The IRB must include at least one scientist and one non-scientist
- * The IRB must include at least one community member (someone not directly affiliated with the institution)
- * IRB members may not participate in the review of any project in which the member has a conflicting interest



- * If an IRB works with studies that include vulnerable populations (e.g., children, prisoners, etc.), the IRB should have members who are familiar with these groups
- * The members must have experience, expertise, and diversity in order to make an informed decision about the research being reviewed

Responsibilities

The purpose of an IRB review is to approve new research studies and to monitor, by periodic review, ongoing research studies. This review assures appropriate steps are taken to protect the rights and welfare of human subjects in research. When conducting a research study the following documents are submitted to the IRB for review:

- * Protocol document including all amendments
- * Informed consent modified per institution requirements
- * Subject recruitment materials (advertising)
- * Written information to be given to the patient (questionnaires)
- * Investigator Brochure
- * Safety Information

In addition to the study specific documents an IRB must also have access to:

- * Investigator's curriculum vitae and credentialing
- * Institution's assurances and credentialing

Why are IRBs Needed?

In addition to the past history of abuses mentioned previously, there are a number of other atrocities that have taken place throughout history. IRBs aim to ensure that only ethical and scientifically valid research is implemented. There are also ethical concerns related to the nature of research in some fields of study such as genetics research. IRB review of such research help to ensure adherence to the ethical values and underlying research principles. The increase in the number of researchers has become so large that self-policing isn't as practical as it may have once been. This increase in the number of researchers in turn increases the possibilities for conflicts of interest and the pressure to publish results.

IRB oversight eases concerns by the general public about the responsible conduct of research



**August 2008: Cancer Clinical Trials – Ethics & Safety
"Consent Forms"**

**by Patrick G. Beatty, MD, PhD; Medical Oncologist, Montana Cancer Specialists;
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The goal of the Consent Form is to provide enough information on a medical treatment so as to allow the patient to make an informed decision about whether he/she wishes to proceed with the treatment. These forms are part of every research protocol, and in many cases, standard of care treatment plans. The forms are reviewed carefully by an Institutional Review Board (see accompanying essay) to make sure that the form is easily understandable. There are often other levels of review, including reviews to be certain that all the known risks of the treatment are indeed included. If the patient has a language barrier, this needs to be addressed before the patient signs a form.

Over the years, the forms have tended to get more detailed and complicated. One reason for this is that the treating or research institutions in charge of the delivery of the prescribed medical care are often instructed by their institution that all the language in the form must be compatible with legal language. This can sometimes be at cross-purposes with making the form easily understandable to the patient.

It is very important that the patient (and hopefully family and/or friends of the patient) carefully read the form, underline parts that are unclear, and write down any questions. There then should be a detailed session with the treating physician to make sure all aspects of the proposed treatment, and its possible complications, are understood.

**August 2008: Cancer Clinical Trials – Ethics & Safety
"Study Design"**

by Grant W. Harrer, MD, Co-Principal Investigator of the Montana Cancer Consortium and Medical Director of the Sletten Cancer Institute, Great Falls, MT

The August Forum will consist of five essays addressing the ethics and safety issues involved in cancer clinical trials. This one is devoted to such issues embodied in the study design itself.

PROTECTION OF PARTICIPANTS:

There are three ethical principles that guide clinical research:

1. **Respect for Persons:** Treatment of each person as autonomous (able to make their own decisions given complete information to do so)
2. **Beneficence:** Awareness of the potential conflict between the good of society vs. the good of the individual



3. Justice: All persons must be treated fairly and all must equally share in the benefits and risks of the research

ETHICAL NORMS FOR CLINICAL TRIALS:

Recall that a "protocol" is a recipe or blueprint for the specific study or investigation at hand. From the ethics standpoint, sound study designs must take into account:

- Randomization or sharing of risks
- Proper use of placebo
- Equitable selection of participants
- Processes to monitor the safety of interventions
- Competent investigators
- Informed consent – see separate essay regarding this topic
- Oversight
 - IRB (Institutional Review Board) – see separate essay regarding this topic
 - DSMB (Data Safety Monitoring Board)

Let's break each of these down a bit ...

Randomization is a method used to prevent bias in research; a computer or a table of random numbers generates treatment assignments, and participants have an equal chance to be assigned to one of two or more groups (e.g., the control group (current standard of care) or the investigational group (a new treatment). Randomization is important to have the groups being compared to be as alike as possible. This provides the best way to prove the effectiveness of a new agent or intervention.

A fundamental principal here is that the data that currently exists regarding the investigational treatment must have led researchers to hope and have reason to believe that it will be better than the standard treatment. Thus, within the limits of currently available human knowledge, the worst a participant can do is to be randomized to standard treatment. A very important ethical underpinning!

Placebos are often referred to as a "sugar pill" or "sugar infusion". As a point in fact, they rarely contain sugar any more, as it became apparent that sugar itself might influence how a person felt, their laboratory tests, and so forth.

The underpinning here is the well-recognized "placebo effect". That is mind-over-matter effect of an intervention producing benefits or side-effects even though there is no active ingredient. Some clinical studies must control for this "placebo effect" in order to separate out what effects are due to active ingredients and what is a background effect if you will.



Cancer treatment trials very rarely utilize placebos in their design. They can only ethically be used when the disease being treated does not have an established standard of care treatment. If one does exist, it must be the control limb for the study, not a placebo. Absolutely, if a placebo is used, patients must be told of this possibility before deciding to participate.

Prevention trials are an example where placebos are used fairly routinely. For most cancers, there is not an established intervention that prevents the disease. Thus, it is ethical and necessary to utilize placebos in that particular situation. On the other hand, now that investigators in the United States believe tamoxifen and raloxifene have been proven to prevent breast cancer in high risk groups, placebos would no longer be appropriate in the prevention of this disease.

Data Safety Monitoring Boards or DSMBs are neutral third party groups (no connection to the study sponsors or investigators) appointed to periodically monitor the efficacy and safety data of a clinical trial as it is being generated. They have the power to temporarily (allowing for study revision) or permanently stop the study if necessary. This is another layer of safeguard to minimize risk, maximize benefit, and ensure integrity of the data.

**August 2008: Cancer Clinical Trials – Ethics & Safety
"Laws and Regulations"
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Clinical trials evaluating new drugs or devices using human subjects without approval of the FDA are not considered legal in the US. Medical society and / or criminal proceedings can be invoked to reprimand or formally prosecute physicians or investigators who are in breach of FDA guidelines. Technically, trials not federally funded or conducted at sites with federal funding or not conducted with the goal of drug approval by the FDA are not required to submit an Investigational New Drug (IND) application to the FDA. In reality, this comprises a tiny segment of the trials conducted and most of the trials that are not technically under FDA jurisdiction voluntarily submit to the IND process.

The evaluation process includes review of preclinical data. This preclinical data includes information gained from the lab using cells grown in incubators and animal studies. Activity and toxicity profiles are summarized and submitted as a package to the FDA. Critical to FDA review of drugs that are being developed is safety. Before any human trials are conducted, a formal toxicity study must be completed. The key "tox" studies determine the expected side effects from the drug and low, medium and high doses of the drug in relevant animal models. The "lethal dose" is also determined. All doses converted to human equivalents based on weight or body surface area. A starting dose in humans is usually picked at a level several orders of magnitude below that which was found to be lethal in animals.

In addition to preclinical data, a formal clinical study plan must be submitted. The clinical plan must be determined by the FDA to be acceptable, especially in regards to patient safety. The key components are dose, frequency and end points. End points are the variables evaluated in the study such as safety and activity (effectiveness). Early studies are focused on safety while later studies aim for activity. Before a drug can continue in clinical development (e.g., from early phase 1 to phase 2 and phase 3 studies) safety and activity data from earlier trials must be presented and reviewed by the FDA.

Finally, before a drug is allowed into the clinic the manufacturing plan must be evaluated, including the facilities, chemicals, protocols for manufacture, and means of assessing the quality and safety of the final product before introduction into the clinic.

The components above, preclinical, clinical, and manufacturing data, when submitted to the FDA for approval, define what is called an IND or investigational new drug application. Again, for all intents and purposes, no new drug is allowed to be studied in the US without an IND filing with the FDA.

Key to the process of clinical trials is the consent process. Although seemingly intuitive, informing patients that they will be receiving an experimental drug and that they have a right to choose not to participate has not always been the standard operating process. The "Tuskegee" experiments in the mid 20th century in which black men were infected with syphilis without their consent in order to better study the natural history of the disease is perhaps the most infamous example pre informed consent experimentation. The FDA clinical trials process in the US, in fact, was developed in response to studies like Tuskegee. The aim of process is to provide detailed information to potential subjects in order to allow careful scrutiny by prospective participants prior to agreeing to enroll. The informed consent process is designed to protect the rights of human subjects. The FDA has outlined specific information that must be explained carefully to subjects investigating clinical trials. These include: the drug type and expected side effects, procedures (e.g. blood draws and CT scans), time on trial, the experimental nature of the trial, cost (if any) of participation, and who is responsible for trial oversight (e.g. the doctor who is conducting the trial).

These components are carefully evaluated by an institutional review board (IRB). IRBs are a panel of reviewers usually drawn from the local area in which trial is to take place. Non-medical community representatives in addition to a panel of medical personnel are the standard representatives of an IRB. Physicians conducting a trial under review are not allowed to participate in IRB decisions and recommendations. The IRB has the responsibility of evaluating the study (and especially the informed consent process) in regards to protecting patient rights. The IRB also commonly makes suggestions in regards to informed consent language in order to make the document understandable to the non medical subject.

Of late, "conflict of interest" has become a major topic for the evaluation of clinical trials. Currently, physicians who have a financial stake in the outcome of a clinical trial are allowed to



conduct trials as long as they declare the amount of money or stock involved. This includes physicians who are advisors to the drug manufacturer / developer, or sponsor of the drug. Many pharmaceutical companies and medical societies have voluntarily put in place guidelines to require physicians to have no financial conflict of interest or hold only a small financial stake in the outcome of drug development. Congress is currently discussing whether to legislate the degree of financial conflict allowed.

Together, the national guidelines of the FDA in combination with local review of clinical trials by IRBs seek to safeguard patient rights and ensure the integrity of the clinical trials process.

In regards to vitamins, supplements, and natural products, the FDA has no such mandate to review and safeguard prior to introduction of the product to the public market place. In fact, the FDA's role is reactionary (see the "Dietary Supplement Health and Education Act, Congress 1994"). The FDA investigates the supplement industry much in the same way it regulates food. No formal clinical trial evaluation process or specification of amount of active ingredient is required. Manufacturers and marketers are free to make claims and recommendations as long as the entity is classified as a dietary supplement. However, technically, it is unlawful to make specific claims regarding a supplement's ability to cure or treat a specific disease. A huge gray zone exists in regards to what constitutes a formal claim for curing or treating a disease. Many companies simply state the product "may" help to alleviate or treat a certain ailment. This is clearly a regulatory area that continues to evolve. This is a very noteworthy point to make in the field of oncology in which exaggerated claims regarding supplement activity are common without scientific data to provide support.

For more details regarding the FDA and clinical trials please refer to the following web site- <http://www.fda.gov/oashi/clinicaltrials/clintrialdoc.html#fda> and for supplements <http://www.fda.gov/consumer/updates/supplements080408.html> .