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DEPARTMENT OF MEDICINE

TRAINING COURSE FOR CLINICAL RESEARCH
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INTRODUCTION

Clinical trials, whether therapeutic, device or psychological/behavioral, must be performed to certain ethical and functional standards. The history of clinical trials goes back to biblical days. The era of modern clinical trials in the United States began in the early 1900's when Congress passed the Food, Drug and Cosmetics Act, and the Food and Drug Administration was created (1912).

Over the next several decades, clinical trials grew in popularity as a means of testing medical theory, became multi-centric and multi-national in scope, but abuses to the human subjects in some of these trials were brought to light. The most infamous of these abuses were described during the Nuremberg War Crimes Trials after WWII wherein concentration camp inmates described being experimented on in ways that had no potential beneficial outcomes.

Because of this, in 1947 the **Nuremberg Code** was established, which outlined rules for the protection of human subjects. This Code requires: voluntary consent to participate in a trial; the right to know what will be done in the trial; and the right to stop participating in a trial. But most importantly, the Nuremberg Code requires that ANY clinical trial performed on human beings must have the potential for benefit to the subject or society, and the risks involved must be proportionate to the potential benefit.

To further assure that clinical trials were managed properly, in 1964 the World Medical Association developed a set of principles titled the **Declaration of Helsinki**, in which a code of ethical conduct by all those involved in the management of clinical trials was detailed. This ethical standard was further expanded in 1979 in the **Belmont Report**, which listed the ethical principals to be adhered to in the conduct of clinical trials of beneficence (does the study benefit outweigh the potential risks involved), respect for persons (voluntary participation and informed consent), and justice (no discrimination in who can be treated or how treated on clinical trials).

Why were these measures adopted? The codes of conduct were deemed necessary and have continued to be expanded and strictly enforced because of abuses that occurred, even in our country and even into the 1970s. The Tuskegee Syphilis Study gave placebo to African American males with syphilis, and even after the discovery of penicillin in the 1940's withheld treatment well into the 1970's. The U.S. government exposed healthy military personnel in the 1960's to high levels of radiation to see what the outcome would be. A trial at the Willowbrook State School in New York gave retarded children hepatitis to test a new vaccine, doing so without informing or asking the parents.

Thus, rules for the ethical conduct of clinical trials are in place and must be followed to assure that the work performed on human subjects gives accurate answers to the scientific questions posed.

TYPES OF CLINICAL TRIALS

Clinical trials are performed for a variety of reasons – development of a new drug or regimen, to gain knowledge of behavioral patterns, etc. – and are performed in a variety of ways.

Investigator Initiated Trials: These clinical trials are designed and directed by the person with the new idea or theory. They are usually designed for limited numbers of subjects, and can be performed at the Principal Investigator’s (PI) institution, or as a multi-center trial with the PI’s institution being the “coordinating center” for better enrollment. Data is collected and statistical analyses performed by the PI.

These studies, if they involve drugs, may have the drugs provided by the manufacturer, and/or the investigator may ask to have monetary support provided by the manufacturer as well. This helps to cover the cost of protocol development, data management and analysis. If this type of funding is supplied, it is in the form of a Grant.

Multi-Center Trials: In a multi-center trial coordinated by UCSF, UC is the recipient of the Grant monies and contracts must be put in place with the participating centers. All outside centers must manage their own regulatory documents in the same manner as UC (i.e. IRB submission, safety reporting), but must also send these documents to UC and the PI at UC must keep the CHR informed of the outside center’s involvement. In addition, UC personnel may be required to audit the other institutions’ data to assure quality of the statistical outcomes.

An important aspect of management of multi-center trials at UC is that UCSF will not act as a drug supplier to the other centers. If investigational agents are to be used in the trial, UC must work with the manufacturer to assure that drug is ordered through and delivered directly to the other centers.

NIH Grants: Another form of Investigator Initiated Trial is an NIH Grant-funded trial. These trials are also the idea of one investigator, but can involve laboratory research as well as clinical research. These are usually competitive Grants, require submission of annual reports detailing progress of the trial. Funds are awarded annually for the term of the Grant based on these reports.

Industry Sponsored: the manufacturers of devices or pharmaceuticals run these clinical trials. Protocols are written, data collected and the study analyzed by the sponsor or a representative of the sponsor (a CRO, clinical research organization). Devices and drugs will be provided when they are being used “investigationally”, and per patient payments, as well as payment for things such as CHR review, annual renewals, pharmacy start-up fee, etc., is provided.

Industry sponsored studies involve new drugs or combinations of drugs/treatments, or new devices. Data is collected and analyzed by the sponsor or their representative, and is ultimately responsible to the FDA for filing of new drug applications or changes of label, or device approval. These studies are monitored closely to try to assure “clean” data, and if a site is a high enroller (or is suspected of fraud) can be audited by the sponsor and/or the FDA.

NIH / NCI / VA Sponsored: These trials are run as “cooperative groups” wherein institutions with similar patient populations participate in trials written by members of the specific NIH institute, the NCI or the Veteran’s Administration. Each local institution will have its own Principal Investigator who oversees the trial at that institution, but the study itself has a central PI responsible for the final analysis of the study. Payment for these studies is at a flat per patient rate determined by the NIH/VA overall operating budget.

Other Types of Studies: In addition to the above types of studies, there are subgroups of studies.

Registry Studies: These studies tend to be for the benefit of the sponsor, usually a pharmaceutical company. They merely collect data on a specific disease or drug and involve no therapeutic intent. However, they are still “clinical trials” and thus require all the same regulatory oversight as therapeutic studies, with subjects signing consents to collect data.

Prevention Studies: These studies are exactly what they appear to be – for the prevention of a disease. They are run in Phases (SEE NEXT CHAPTER) as are therapeutic studies, but start with well subjects or “volunteers”. These studies many times will pay the volunteers for participating, whereas therapeutic studies routinely pay subjects only for travel, overnight stays for treatment, or lost wages.

Compassionate Use Studies: There are two types of Compassionate Use study: the first is the truly compassionate usage of a drug for a patient for whom there is no other treatment available through commercial sources or on an open clinical trial (due to eligibility or where the trial is being run). Usually the patient must have a desperate need for treatment. The physician in charge must get the permission of the drug manufacturer and the FDA to obtain and use the product (usually via a phone call), and then informs the CHR of what is being done. No CHR approval is required – merely informing them. A description of the study, a consent form and FDA forms are sent to the FDA and when the patient no longer requires the drug, a final report of what occurred is sent to the manufacturer, the FDA and the CHR.

The second type of Compassionate Use study is when a new drug has so obviously been beneficial in trials prior to filing with the FDA for approval that the FDA advises the manufacturer to open an ‘expanded use’ or ‘compassionate use’ trial so that patients who could benefit from the drug can still receive it. This type of Compassionate Use trial must still obtain CHR approval, the drug is provided at no charge to the patient, the compensation to the site is minimal but that is because there is very little data collected – usually just dosing and safety information.

Donation Studies: These studies are performed to assist researchers, either from the university or outside enterprises, in obtaining material on which to experiment. This material can be tissue, blood, or urine, and all costs involved in the collection of the material are paid by the enterprise or university, including payment to the donor.

PHASES OF CLINICAL TRIALS

Pre-Clinical trials: Clinical trials begin with an idea that is tested in a laboratory (in vitro) and is felt to be of benefit to the treatment or prevention of a condition or disease. These include those done in test tubes or on animals.

When performed in humans (in vivo), they are done in stages, or phases.

Phase I clinical trials: Phase I studies are the initial clinical tests of new treatments. The major purpose of a Phase I study is either to define a safe dose and schedule of agent or combination of agents or to evaluate the feasibility of combining treatment modalities. Phase I studies are usually designed based on promising preclinical data (in vitro) provided a stable and safe formulation of the agent is available.

Most phase I studies treat cohorts (groups) of patients (typically, 3-6) at predefined dose levels. These studies start at very low doses that were minimally toxic in animals. If that dose is safe, a cohort of patients is treated at a higher dose, with escalation continuing until a maximum tolerated dose (MTD) is defined. Various escalation schemas with successively smaller increases in dose are used, with rapid escalation at lower, presumably more tolerable, doses and slower escalation as the dose increases. The toxicity defining the MTD is based on toxicity found in animal testing, with provisions for unexpected toxicities. A dose for phase II studies is decided based on the MTD; usually, the phase II dose is 1 dose level lower than the MTD.

Phase I studies may also be designed to determine the toxicity of lengthening or shortening an infusion schedule or the interval between treatments, assess supportive care designed to reduce toxicity, and determine an optimum biologic dose (OBD, i.e., the dose associated with the maximum desired biologic response for which toxicity is still acceptable).

The schedule of drug administration in Phase I studies is determined from preclinical testing. Common schedules include administration once every 2 to 4 weeks, administration for 5 consecutive days every 3 to 4 weeks, or daily dosing. Schedules may also be based on maintaining a certain drug level in the blood, determined by pharmacokinetic (PK) blood testing.

Scheduling may involve varying the length of intravenous infusion. Commonly, a study employs one schedule; however, some studies compare multiple schedules within the same study. Agents may be given intravenously, orally, intra-peritoneally, intra-vesicularly, or through other routes. Sometimes, investigators will randomize patients to multiple doses, schedules, or routes of administration to more quickly assess tolerance to various dosing routines and to rapidly follow up on the more promising one. Agents that are commonly used by one route or on an established schedule may return to Phase I testing in order to determine a safe dose by another route or on a different schedule because an investigator has an important lead about how to improve the agent's effectiveness or reduce its toxicity. Also, Phase I studies are employed to test the feasibility of combining drugs or different modalities of treatment (for example, chemotherapy with radiotherapy).

Phase II clinical trials: Once the MTD is known, if it seems the drug or therapy MAY be beneficial, Phase II trials are begun to test efficacy. Phase II trials include a larger number of subjects, usually between 20 and several hundred per trial. Further determination of toxicity is the second major purpose of Phase II studies. In most cases, fewer than 100 patients have ever received the new treatment prior to phase II testing. Phase II studies normally involve several trials that collectively treat hundreds of patients with different conditions or diseases. Unusual or chronic toxicities, which are often missed entirely in Phase I testing, may appear during Phase II testing. This is considered when deciding whether the therapy should be further evaluated in Phase III studies, along with the statistical analysis done on the efficacy of the therapy.

The dose and schedule for Phase II trials are taken from the Phase I studies. In the absence of unacceptable toxicity, some Phase II trials allow patients to continue treatment as long as they respond to therapy or remain stable; other Phase II protocols limit therapy to a specified number of treatments. Following treatment, patients are usually followed for outcome, i.e., for disease recurrence or progression, for survival, and for evidence of late toxicity.

An adequate number of subjects need to be treated to determine the level of therapeutic activity. If no responses are seen in 2 trials, the therapy is usually considered inactive for that disease. If responses are seen, the number of subjects studied is increased to more precisely define the response rate.

Some clinical trials combine Phase I and Phase II study designs within the same protocol, and subjects treated at the recommended Phase II levels during the Phase I portion may be added to the statistical pool for the Phase II portion. Newer statistical approaches to Phase II studies include randomization of subjects to 2 or more treatment arms, each testing a new agent or therapy. The agent producing the highest response rate, even if the response rate is not significantly higher than that produced by other agents or therapies, is chosen for Phase III testing.

Phase III clinical trials: Phase III studies are designed to compare one or more treatments. A new drug/drug combination or treatment modality may be tested against one of proven efficacy. Phase III studies often have multiple endpoints. Overall and disease-free survival is nearly always endpoints; differences in response rates, toxicity, patterns of disease recurrence, and quality of life might also be endpoints. At the conclusion of a properly designed and conducted Phase III study, the new drug/drug combination or therapy will be found to be inferior, equivalent, or superior to the standard treatment with respect to the major endpoints. The degree of difference will be known, and the statistical significance will be estimated.

In Phase III studies, subjects are randomly allocated to the treatment options to help ensure unbiased comparison of the treatments. The numbers of patients who are treated with each regimen depends on the number of major events (usually recurrence or survival) predicted to occur during the course of accrual and follow-up. Anywhere from 100 to several thousand subjects may be required, and accrual to the trial may take 2-5 years or more. Studies must be designed to account for major prognostic categories by either entering large numbers of patients or by stratification on the basis of known prognostic factors. For example, a phase III study in

breast cancer may randomize premenopausal and postmenopausal women separately. In spite of stratification and randomization, some studies will enroll more patients with good prognosis in one arm than in the others. In such cases, statistical techniques exist to retrospectively "balance" the treatment arms for prognostic factors.

In Phase I, II and III clinical trials, the sponsor of the trial provides the investigational agent or therapy to participants. This is because the drug or therapy is not approved by the U.S. Food and Drug Administration (FDA) and thus cannot be billed to or paid for by insurance. If a Phase III trial includes drugs or therapies that are FDA approved, these are not provided.

Blinding and Placebo-Controlled trials: In Phase II and III trials, placebos may be used to better assess the efficacy and benefit of one drug over the other. Placebos are NEVER used if there is a therapy for the condition or disease being studied – only if the standard of care is no treatment at all (i.e. maintenance therapy or none following primary therapy for a disease). Blinded trials are those where multiple treatment Arms are involved where to avoid bias those involved in the direct patient care do not know which therapy a subject is receiving. Blinded trials can involve all subjects receiving some treatment or the use of a placebo for some subjects.

Phase IV clinical trials: Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities such as the FDA, or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples include Baycol and Lipobay, Rezulin and Vioxx.

REGULATORY AGENCIES

Drugs and therapies must be “approved” wherever they are to be used. Something approved in this country cannot automatically be used in Europe or Japan. Each country has its own rules for approval and oversight of usage. If a clinical trial has been done with a new drug or device, the appropriate regulatory agency for the country where the trial was conducted reviews all study data before allowing the drug or device to proceed to the next phase of testing, or being approved for sale and use.

In the United States, the **FOOD AND DRUG ADMINISTRATION (FDA)** oversees all medical trials of drugs and devices trying to gain approval for commercial use. Not only is the data collected from each investigator involved in the trial looked at, but also the investigator can be audited to assure that the data is correct. Irregularities in the conduct of these trials can lead to debarment, fines and/or imprisonment of those involved – including CRCs if they were involved.

The FDA regulations for clinical trials are set out in the Code of Federal Regulations (CFR) (<http://ecfr.gpoaccess.gov>) Title 21. The important sections of the CFR pertaining to an institution conducting clinical trials are:

Part 11: Electronic Signatures

Part 50: Protection of Human Subjects

Part 54: Financial Disclosures

Part 46: Institutional Review Boards

Part 300: Drugs (New Drug Application, Marketing, etc.)

Many studies of drugs and therapies are sponsored by one of the **NATIONAL INSTITUTES OF HEALTH**. In these instances, that specific division involved in the condition or disease being studied has direct responsibility for assuring that the clinical trials are correctly run. (<http://www.nih.gov>) Also, the **VETERANS ADMINISTRATION** oversees all clinical trials run in the VA facilities across the country. (<http://www.va.gov>).

An **INSTITUTIONAL REVIEW BOARD**/independent ethics committee (IRB/IEC) is a group that is formally designated to approve, monitor, and review biomedical and behavioral research involving human subjects. In the U.S., FDA and HHS regulations have empowered IRBs to approve, require modifications to secure approval, or disapprove research. An IRB performs critical oversight functions for research conducted on human subjects that are *scientific, ethical, and regulatory*. IRBs were developed in direct response to research abuses earlier in the twentieth century. IRBs are independent bodies and vary widely in what they require to protect subjects' rights.

DATA SAFETY MONITORING BOARDS. Many randomized clinical trials are double blinded, i.e. no one involved with the trial knows what treatment was given to the trial participant. This includes the participant, their doctor, and even the study personnel at the company that is sponsoring the trial. There are many extremely good reasons to conduct a trial in this manner and usually only after the trial database is finalized is the blind broken and the true treatment assignments disclosed. The exceptions to this rule include when a study has a crossover arm (patients failing one therapy are allowed to go to the other) where one of the arms is a placebo, or if the next treatment to be given to a patient depends on knowing which treatment was received on the blinded trial.

However, these trials may go for years and there is justifiably concern about enrolling subjects and exposing them to an unproven treatment without someone overseeing results. The company sponsoring the trial is blinded, so they can't perform this service. Even if they had some people who were unblinded to the results, they would be in an awkward position between concern for their corporate interests and concern for the trial participants.

The DSMB is a group (typically 3 to 7 members) who are independent of the company sponsoring the trial. At least 1 DSMC member will be a statistician. Clinicians knowledgeable about the disease indication are represented, as well as clinicians knowledgeable in the fields of any major suspected safety effects (e.g. nephrology, cancer, cardiology). A few long, visible trials may include an ethicist or even a representative from a patient advocacy group. The DSMB will convene at predetermined intervals (3-6 months typically) and review unblinded results, i.e.

results split by experimental and control arms. The DSMB has the power to recommend termination of the study based on the evaluation of these results. There are typically 3 reasons a DSMB might recommend termination of the study: safety, outstanding benefit, and futility.

CLINICAL RESEARCH ORGANIZATION (CRO): Many sponsored clinical trials have independent organizations – CROs – manage the trials to prevent any bias in the results. These CROs can manage parts (i.e. only the data base) or all aspects of a clinical trial. CROs are required to operate under FDA guidelines and sections of the CFR relate specifically to these regulations. They have their own operating policies and procedures, which must be followed as well.

Other international organizations or associations that regulate how clinical trials are run include:

The **CIOMS** Guidelines, formally known as *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, is a set of ethical principles regarding human testing. Created in 1993 by the Council for International Organizations of Medical Sciences (CIOMS) and updated in 2002, these 21 guidelines (15 in the original report) address issues including informed consent, standards for external review, recruitment of participants, and more. The Guidelines are general instructions and principles of ethical biomedical research.

The **EUROPEAN MEDICINES AGENCY (EMA)** is a European agency for the evaluation of medicinal products. Until 2004, the European Medicines Agency was known as The European Agency for the Evaluation of Medicinal Products. Similar to the FDA, but without FDA-style centralization, the EMA was set up in 1995 with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, in an attempt to harmonize (but not replace) the work of existing national medical regulatory bodies. The hope is that this plan will not only reduce the \$350 million annual cost drug companies incur by having to win separate approvals from each member state, but also that it will eliminate the protectionist tendencies of states unwilling to approve new drugs that might compete with those already produced by domestic drug companies. The EU is currently the source of about one-third of the new drugs brought onto the world market each year.

The **UCSF** has its own regulatory requirements when it comes to clinical trial management. The IRB here is called the **Committee on Human Research (CHR)** and has its own set of rules and regulations, forms for submission of the various documents required by clinical trials, and information to help you through the process (<http://www.research.ucsf.edu/chr/Guide/>). They also offer a training program for new CRCs (<http://research.ucsf.edu/chr/Train.asp>). (Please refer to Appendix K for comprehensive information on the CHR.)

FINANCIAL ASPECTS OF CLINICAL TRIALS

Clinical trials take time and effort for an institution to run. Whether it is an investigator-initiated trial, a trial run under the aegis of the NIH or one of its branches, or a trial sponsored by a pharmaceutical company or device manufacturer, financial backing is very necessary.

“In clinical research, a site needs to anticipate that the time and effort necessary to successfully complete a study will be significantly greater than it would be to treat a similar number of regular-practice patients. The site must negotiate a budget that provides adequate reimbursement for that extra time and effort”

Dr. David Ginsberg, The Investigator’s Guide to Clinical Research, Centerwatch

Types of Funding

If a study is sponsored by the NIH or one of its branches, such as the National Cancer Institute (NCI), there is a fixed per patient budget allocated. The NCI’s Cooperative Group System that sponsors many trials in North America pays a flat \$2,000 per patient no matter how complex or what data is to be collected. Some additional funding may be available IF a site is considered a “member institution” and thus qualifies for some salary support.

Some studies from the NIH and Industry (large investigator initiated studies with significant ultimate revenue potential for the sponsor) are funded through Grants, for which detailed budgets must be submitted, negotiated, approved and used exactly as submitted.

Investigator Initiated studies can sometimes be funded if the company making the device or agent is interested in obtaining new markets for their product. However, these studies are usually funded by small Grants that only defray some of the trial costs.

Pharmaceutical company and device manufacturer sponsored studies have significant funding available with which to conduct their clinical trials. They offer sites draft budgets, which the sites can then use to negotiate prices based on their particular costs of overhead, test/procedures, and salaries.

A research program cannot function without having its costs met. Therefore, most institutions involved in clinical trials have a mix of the different types of trials funded through the mechanisms above. While studies funded by Investigator Initiated Grants cover only a small portion of the trial costs, NIH and larger project trial grants should cover all expected costs. Pharmaceutical and device company trials are also adjusted to meet all costs, including paying for clinical trial tests/procedures that are being done solely for research and are not standard of care (SOC) for the disease or condition. In addition, studies like prevention studies must pay for all trial costs as everything in these trials is considered outside of SOC.

How do you develop a clinical trial budget? First you must identify your resources; do you have all the equipment necessary or do you need to include these costs in the budget? Do you have to out-source some of the tests and/or procedures (such as specialized laboratory tests)? What do the non-standard of care tests and procedures cost? You must work with your Research Services Analyst (RSA) and Industry Contracts negotiator to ensure that you will receive payment for everything required to complete the trial. Then, determine how much work and time is involved. Is extra staff required?

Identify Procedural Costs: Obtain a list of charges for routine procedures. (If services are provided by UCSF Medical Center, contact Accounting at 353-4802). With the help of the PI, determine which tests/procedures are standard of care (SOC). New Medicare regulations suggest that the PI should sign off on this in case of audit. (SEE SAMPLE BILLING FORM)
If investigational, determine the % discount that will be offered as a research rate.

Work with the Research Service Analyst for your division: The RSA oversees the submission of the proposal and contract to be executed. The RSA facilitates the process of budget development, execution of non-refundable pre-clinical trial fee (at least \$8,000) to cover the PI's time in developing/negotiating the protocol, the CRC's and Contracts' time in negotiating the budget with the sponsor. Always include ancillary fees (pharmacy set-up, CCRC, CHR, renewals/amendments, advertising, outside vendors, screen failures, etc.)

Workload Costs: Determine how many patients will potentially be enrolled. Determine how many visits for each patient. Determine how much data must be collected. Determine if data will be on paper or through electronic case report forms (e-CRFs). Determine if there is any training required (e-CRFs, special equipment). Determine if extra work will be required to Invoice for payments

Remember, budgets and contracts can be renegotiated during the trial if expenses increase beyond the initial budget. Reasons may include the number of patients enrolled has increased (increase the number of screen failures to be paid for), if extra tests are required (whether or not they are SOC or investigational only), and/or if the prices of outside vendors or services increases.

A CRC's role after a trial is running is also to monitor the appropriateness of billed charges to the trial and to third party payors, which includes establishing the correct accounting for services provided and the registration of enrolled patients. These responsibilities are integral to meeting the federal and CMS compliance requirements established for clinical trials. *(Please refer to Appendix L for a comprehensive detail.)*

OPENING A CLINICAL TRIAL

Before beginning any clinical trial, a number of things must be in place. No trial can be started without the proper regulatory, financial or staffing in place, contracts signed, and if drug is involved, without the drug. No clinical trial performed on human subjects can begin without approval (or exemption if a trial will be for data collection only) from an IRB, financial support of the trial determined and obtained, and sufficient staffing to manage the trial must be in place. A drug will never be provided to a site without all of the above being in place.

Industry Sponsored Trials

Sponsored studies will be offered by manufacturers of devices or pharmaceuticals to a Principal Investigator (PI) who must prove his competence and ability to manage a clinical trial. Before the trial documents, including the potential protocol, can be obtained, a **Confidentiality Agreement (CDA)** must be signed in the name of the University. This can only be done by

someone in the Contracts & Grants Division. Once the sponsor, the Protocol, Investigational Drug Brochure (IB) if applicable, receives this a sample Informed Consent Document, and outline of what regulatory documents are required will be sent.

At this time, you should be sent or request a copy of the draft contract and budget for the study, so that work can begin on these documents. As well, looking at the draft budget at the start of the project may help determine if the PI will indeed participate. For example, if the draft budget does not appear to cover costs, and discussion with the sponsor gives the impression that nothing can be done to change this, the trial should be declined (unless there is a significant scientific reason for doing the trial anyway).

In addition, it is not unusual for a **Site Visit** (SV) to be required to officially “select” a site for the trial. This SV requires a tour of the facility to assure the sponsor that there is adequate space to conduct the trial, that the required equipment (i.e. -80 freezer, lab facilities, treatment area) are in place, and that through discussion it is shown that the PI and site personnel have the interest and time to conduct the trial.

Many sponsors also have off-site **Investigator Meetings** where the clinical trial is discussed among all the Investigators/Coordinators to be involved in the trial. It is also required by the FDA that every trial have an on-site **Initiation Meeting** before beginning subject enrollment. This meeting will review with site personnel the details of the study, but in addition will:

- Check regulatory documents,
- Assure that the devices or pharmaceuticals to be used arrived in proper order and that the custodian of the investigational product knows proper management of them,
- Review with the CRCs how to collect the data properly – whether on paper or through e-data collection systems,
- Assure that all required study supplies – case report forms, send-out lab kits, patient diaries, special equipment – have arrived,
- If an Interactive Voice Registration System (IVRS) is to be used, assure that all persons needing access (PI, study coordinator, pharmacist) are trained in its use.

As many of the people to be involved in the clinical trial as possible should attend this meeting so as to ask and have answered any questions that come to mind. The PI and study coordinator, however, are required to attend, but nursing personnel who might be involved in patient care on the trial, lab personnel if special studies are to be done, and the Investigational Pharmacist should also be invited.

Regulatory Submission: once a site has been selected to be part of a clinical trial, the sponsor must receive the following documents:

- Investigator Documents: CVs for PI and all sub-investigators, as well as their medical licenses
- Statement of Investigator: The 1572, a federal form required to explain by whom and where the trial will be conducted and listing the Investigator's responsibilities
- Laboratory Documents: the Clinical Laboratory Improvement Amendments (CLIA) and Clinical Laboratory License from the State of California. College of American Pathology

(CAP) license is not required even though some sponsors request them, since to obtain the CLIA a lab must be certified by CAP first. Only 2 lab certifications are required.

- In addition to the certificates, the normal ranges for all tests to be performed on blood and urine throughout the study (<http://labmed.ucsf.edu/labmanual/mftlng-mtzn/test/newtestreq.html>) are required.
- IRB Documents: CHR approval for: initial approval (and annual renewals, amendments/revisions later); membership list/Assurance of Compliance; approval of any advertising materials to be used; and/or patient hand-outs (i.e. diaries, information sheets on the treatment).
- Site Informed Consent Document: The Sample Consent sent by the sponsor is amended to conform to the site's IRB requirements. This **MUST BE APPROVED** by the sponsor prior to submission to the IRB, and any IRB-required changes must again be approved by the sponsor.

An easy method of assuring that everything except those documents needing IRB approval are sent is having on hand a supply of each type of document (i.e. a packet of all CVs/licenses of investigators to be included on your trials or all necessary lab documents). This allows turn-around over night, which is looked on with great favor by sponsors and CROs, and results in the site/PI being asked to participate in other trials with that sponsor or CRO as they come along.

Regulatory Binder: Each site conducting a clinical trial must keep (permanently) a binder(s) containing every piece of documentation pertaining to the trial. This includes:

- ALL written correspondence with sponsor, including e-mails
- Copies of all the regulatory documents submitted
- Approved Informed Consent Document (NOTE: some IRBs stamp and return to the Investigator the final approved consent – UCSF's CHR does not do this)
- Notes to File, which explain unusual situations at the site
- Special Documents on a trial by trial basis (i.e. Screening/Enrollment Log, Monitor Sign-In, Delegation of Authority)

Investigator Initiated Trials

Since the “sponsor” of the trial is the Investigator, everything begins with the PIs concept, which may or may not be required to have collegial approval. A protocol is written, a consent form drafted, and some method of capturing the trial data developed (this may be the development of case report forms or spread-sheets). These documents all require CHR approval, and there may be other approvals required, such as the CCRC's IRB or the VA's IRB if the clinical trial is to be run in their facility (SFGH accepts our CHR approval). In addition, some disciplines, such as oncology, may have scientific review committees that must approve the trial.

As described above, regulatory documents must be maintained and contracts/budgets applied for and negotiated.

INDs: Another important issue that must be discussed when Investigator Initiated studies are being developed is whether or not an "Investigational New Drug" or "IND" Application for Exemption must be filed with the FDA. Every new drug is assigned an IND number before it is to be used in humans. This IND number stays linked to the drug as long as it is being "experimented" with, even if and after it obtains FDA approval for use. For any new use, the IND number must be referenced.

If an Investigator plans on using a drug in an experimental manner in the Investigator Initiated trial, he must obtain permission from the manufacturer of the drug to do so, and they must notify the FDA that they are giving permission for the drug's use under their IND. The Investigator must then obtain either official permission to hold the IND or obtain an IND exemption.

Instructions on submitting to the FDA in this regard can be found at the FDA's website (<http://www.fda.gov/cder/>) and in 21 CFR 312.2(b)(1) (<http://ecfr.gpoaccess.gov>). In addition, UCSF's CTSI Department can assist you in filing for an IND. Contact Marlene Berro at Marlene.Berro@ucsf.edu.

Working with the Committee on Human Research (CHR)

The CHR requires that anyone utilizing their IRB complete an Ethics training course (CITI Training...SEE WEB ADDRESS previously given). In addition, their website gives all the information required to understand how to work with them to achieve a clinical trial approval.

CRCs, as well as all PIs, must be trained in the use of the iMedris if they are to handle CHR submissions. For training or questions, contact Melanie Mace at 376-9839 or Melanie.Mace@ucsf.edu.

Basically, the process is as follows:

1. The CHR New Submission Application is prepared in the iMedris system. Use the protocol to "copy and paste" sections to be entered into the various parts of the iMedris Application form.
 - a. Make sure to list anyone who will work on the trial in a significant fashion (sub-investigator, CRC, outside consultants, etc.) in the Key Personnel section and make sure to list yourself in the Contact section so you will be notified any time there is an Approval, renewal due, etc.
2. When the Application Form is completed, the ICF, Investigator Brochure, any attachments (Questionnaires, Advertisements, Patient Diaries, etc.) are attached in either "Informed Consent" or "Other Documents".
3. The "packet" is SUBMITTED for SIGNATURE by the PI.
4. Once signed, it will be assigned to a reviewer.
5. Reviewer can request changes and you will be notified quickly.
6. Make changes as requested and resubmit (you will be allowed to sign off on the changes).
7. You will be notified when Approval has been obtained or when a Contingency or Return has occurred.

The process for Annual Renewals and Modifications is a little more complex, but basically you go into My Studies and select the study that is to be worked on. The correct form appears and you complete as you did with the original submission. In the case of a Modification, you will chose “edit” to get a new version of the original Application, you will download and replace a revised protocol and/or consent, etc.

Original submissions and Annual Renewals must be signed off on by the PI of the study. They will receive an e-mail notification for this. On modifications, however, if you are listed as Key Personnel (which you should be), you will be the only signator required.

With regards to IND Safety Reports received from sponsored studies, the CHR has very definite rules that they ARE NOT to be reported, even though sponsors tell you this is required. There is a statement on the CHR website to this effect and explains how safety reports (SAEs from other institutions) are to be handled. This can be addressed with the sponsor with a Note to File, explaining that the CHR will be notified (using a log sheet listing all safety reports received and/or SAEs occurring since the prior report) when annual renewals or amendments to the protocol are submitted. Further, the CHR allows 10 days for notification of SAEs (unlike the usual “within 24 working hours”), but again ONLY WANTS SAEs that are directly related to study treatment. This, too, should be noted in a Note to File for the sponsor, since this is outside of normal SAE reporting.

Working with the CTSI's Clinical Research Center

If you are conducting trials requiring special testing, i.e. pharmacokinetic studies (PKs) or pharmacodynamics (PDs) that are required when Clinics are not open or if the patient is an In-Patient, you will need to work with the CCRC. These specialized Units are on 12 Moffitt, at Mt. Zion, the VAMC and SFGH, and are staffed to work with research patients. The staff is trained in the importance of conducting all aspects of a protocol in accordance with the protocol specifications and in timely fashion. They have their own IRB to which you must apply and receive approval from, and forms that explain what will be required for the clinical trial.

If you are working with the CCRC, be aware that there is a \$1,000 fee for their IRB review, as well as fees for the work done by the staff for the trial. It is usually best to get an overall cost per patient stay in the Unit to include in the clinical trial budget (along with the CCRC's IRB fee) and then delete the fees proposed in the study budget for the work being done in the CCRC. You must also submit any Amendment or Revision to the protocol to them.

You will need to develop very specific Standing Orders for each trial, which must be approved by the Nurse Manager of the Unit. Also, copies of the signed ICF must be on the Unit before they will treat a patient.

In addition, it is advisable to invite the Nurse Manager from the CCRC to the study initiation meeting if one is to be held, and/or inform the CCRC staff by having a meeting with them to discuss the protocol procedures.

CONDUCTING THE CLINICAL TRIAL

Once your clinical trial is open to enrollment, Good Clinical Practices (GCP) rules (SEE ATTACHMENT) must be followed to assure ethical management of the trial and produce data that is verifiable and can thus be used to change treatment of patients.

Consenting: The first and most important of these rules is that any subject asked to participate in a clinical trial must be consented before any trial procedures are undertaken. This does not apply to those tests and/or procedures that would be done for standard of care for the condition being studied, but does apply to everything that is done for the research alone. A copy of the signed consent must be given to the subject, another placed in the medical record and/or Clinic chart, and the original kept with the study records (case report form binder or shadow chart). If at any time the clinical trial is amended where there is a change that could affect the subject's willingness to continue to participate (i.e. additional tests/procedures, length of treatment, new risks to the treatment) the subject must be re-consented with a new CHR-approved consent form. Consent forms must have the UCSF HIPAA form attached, and subjects must be given a copy of the CHR's Research Subject Bill of Rights.

In addition, there is a requirement that consenting to a trial be documented in the subject's records. This can be in the medical record, Clinic chart or in a shadow chart, and should be done by the person obtaining consent. This should be done as soon as the consent has been signed.

If your patient does not speak and/or read English, the CHR has, on their website, the Bill of Rights in many other languages. Using the form in the patient's language and a Certified Translator satisfies the CHR's requirement as "Short Form" consenting. All you need do is download the one needed and give to the patient, documenting that it was given in the patient's language.

Enrollment: Once a subject has been consented, all required screening tests/procedures must be completed BEFORE the patient is enrolled to the study. If a test/procedure result must be known to judge eligibility, those results must be obtained prior to study enrollment to assure the subject is "eligible".

A good way to assure eligible patients is to have a 2nd person, another CRC or Investigator, go over the eligibility criteria AND the schedule of events (which lists each individual test that must be performed) so that nothing is missed. An ineligible patient cannot be included in the study's analysis but since most studies are on an "intent to treat" basis, uses up one of the subject slots. And, enrolling ineligible patients can cause sponsors to close the site and/or refuse to give future trials. On an investigator initiated trial, an ineligible patient can result in CHR penalties, or if a Data Safety Monitoring Committee is involved (as is the case with all investigator initiated trials in Oncology), to stop further research by the PI or Practice.

If a test/procedure that is required is slightly out of the required windows of time (by a day or two), or if a required eligibility test is slightly out of range, it may be possible to obtain a "waiver" or exemption from the study sponsor. This is true for sponsored studies and investigator initiated studies alike and is based on safety for the subject. If an exemption is

granted, this must also be approved – before enrolling the subject and beginning therapy – by the UCSF CHR (this is done as an expedited review).

Data Collection: All data points in the case report form, all tests/procedures required by the clinical trial, and all toxicities must be documented before being entered into study records. (The one exception to this is when a questionnaire is required to be completed by the subject.) The FDA defines a “source document” as the first place something is recorded. If in going through a subject’s records you find conflicting information, it should be clarified and a new statement recorded.

When doing data, remember a few important facts:

- NEVER use white out in a medical record or data form. This can be interpreted as fraud
- When making a correction to data that has been entered, use a single line strike-thru and initial and date the correction
- Start at the top of a page and work your way down. If there is a data point to which the answer is unknown, use a “flag” at the side of the item to alert yourself to an incomplete place. You can always go back later to complete.
- If you have had to obtain reports from IDX or UCare, print them out and keep in a shadow chart or the pocket of the case report form binder as your documentation.

Monitoring and Auditing: There is a distinct difference between monitoring and auditing. Monitors work for a study sponsor with the primary goal of having accurate, quality data submitted about subjects enrolled to clinical trials. They are there to assist the CRC in collecting the proper data in the format the study sponsor requires for their data base. A Monitor is required to: do 100% verification of all data being submitted, to check the Investigational Pharmacy if investigational drugs are being used to assure compliance with Drug Accountability, to meet with the PI of the study on a routine basis to discuss how the trial is being handled, and to assure that all regulatory matters are adhered to and documents submitted with duplicates kept in a regulatory file.

Auditors, on the other hand, are looking for problems with the study's management. An auditor usually only goes through some of the cases enrolled to a study, as well as 100% of regulatory issues and Investigational Pharmacy management. While there will be the ability to fix any problems found once the audit has been completed, the results of audits can impact whether a site and/or PI is offered other clinical trials in the future. If an FDA audit is scheduled, the company sponsoring the trial will always want to audit the site before this occurs to try to forestall any problems being found. Sometimes sponsors audit to see whether their Clinical Research Organization (CRO) supplying the monitors is doing a good job or not, and sometimes they audit a site just to assure themselves that their selected sites are doing good work.

ADVERSE EVENTS

In Clinical Trials, Adverse Events are reported to gather information on the potential toxicity of the treatment or drugs being given. Toxicity in one patient may or may not be related to the drug or therapy, but in reviewing toxicities from all the patients enrolled to the trial, a pattern can emerge. This is how the package insert of drugs, or the known risks of treatment or a device, is developed.

An adverse event, or AE, is defined as: “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. More simply put, it is **any change from the patient’s baseline condition**, which may or may not be side effects (toxicities) of the therapies given. Thus, all symptoms of disease or medical problems present at baseline must be detailed if a clear picture is to emerge.

To determine how severe an AE is, clinical trials use a grading system to categorize toxicities. In oncology, the Common Toxicity Criteria (CTC) version 3.0 is used (a listing of 240 different potential toxicities with descriptions of each grade from 0 [no toxicity] to 5 [death]. Clinical trials for other diseases or for conditions not using or listed in the CTC are graded as mild, moderate, severe or life threatening. An important thing to remember: sponsors of clinical trials want causality of the toxicity determined. This can only be done by an investigator involved with the clinical trial, even if the cause is obviously not associated with the drug or treatment.

One point to remember when listing AEs: DO NOT use adjectives. The grade of the toxicity describes the severity. Thus, do not list “severe pain”, merely “pain”.

The following scenario lists baseline conditions AND adverse events.

Mrs. Jones comes to her doctor’s office complaining of cough, chills and fevers, diarrhea, and muscle aches and pains. After examination, Dr. Smith tells Mrs. Jones she has the flu. He prescribes bed rest, aspirin and a cough medicine.

After taking the cough medicine, Mrs. Jones becomes nauseated and vomits many times. Her fever, which had been 99.9 degrees, rises to 103.0 degrees, and because of the vomiting and diarrhea she becomes dehydrated and requires hospitalization for IV fluids. After an overnight stay lasting 16 hours she is discharged in good condition, with all symptoms of the flu having resolved.

In this scenario, **the baseline condition is flu** (signs and symptoms of a syndrome are not listed; only the syndrome). **The adverse events are: nausea, vomiting, fever** (if a baseline symptom/condition worsens once therapy has begun, that then becomes an AE) **and dehydration**.

In addition to AEs, **Serious Adverse Events (SAEs)** are also tracked in clinical trials. A serious adverse event in human drug trials is defined as: **any untoward medical occurrence that at any dose results in:**

- death
- is life-threatening (an event where the patient is at risk of death from the occurrence)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

In the scenario above, it appears that Mrs. Jones has experienced an SAE (i.e. the hospitalization for dehydration), but in fact she did not. This is because the hospitalization lasted less than 24 hours – The definition of a “hospitalization” in clinical trials requires 234 hours or more of an inpatient stay.

The Code of Federal Regulations (CFR) states that SAEs are required to be reported to the sponsor of a clinical trial “as soon as it is known” by the Investigator or his research staff. Typically, this is an ambiguous statement as is much of the CFR. However, sponsors and cooperative groups have defined this as “within 24 working hours of knowledge of the event”. The report is to be made and signed by whoever has the knowledge and with as much information as is known at the time. DO NOT wait for an official diagnosis or results of a test. All SAEs that are not closed out on the initial report require follow-up reporting when the SAE has resolved or more information is known (i.e. a hospital discharge summary).

In addition, anything that is an SAE is also an AE and must be listed with the AEs on the case report forms.

APPENDIX A

THE NUREMBERG CODE

The judgment by the war crimes tribunal at Nuremberg laid down 10 standards to which physicians must conform when carrying out experiments on human subjects in a new code that is now accepted worldwide.

This judgment established a new standard of ethical medical behavior for the post World War II human rights era. Amongst other requirements, this document enunciates the requirement of *voluntary informed consent* of the human subject. The principle of voluntary informed consent protects the right of the individual to control his own body.

This code also recognizes that the risk must be weighed against the expected benefit, and that unnecessary pain and suffering must be avoided.

This code recognizes that doctors should avoid actions that injure human patients.

The principles established by this code for medical practice now have been extended into general codes of medical ethics.

The Nuremberg Code (1947)

Permissible Medical Experiments

The great weight of the evidence before us to effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each

individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

APPENDIX B THE BELMONT REPORT
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Ethical Principles and Guidelines for the protection of human subjects of research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

**** David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.

**** Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

**** Deceased.*

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Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging

physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes(1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (2) By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the

responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. (3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions.

Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk

without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should

never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence

would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of

systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial,

sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare. Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

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APPENDIX C DECLARATION OF HELSKINI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

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Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or

eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the

specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the

publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
 - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

APPENDIX D
INTERNATIONAL CONFERENCE ON HARMONISATION (ICH)

Technical Requirements for Registration of Pharmaceuticals for Human Use

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- It needs **additional** [references or sources](#) for [verification](#). Tagged since January 2009.
- It may require general [cleanup](#) to meet Wikipedia's [quality standards](#). Tagged since September 2007.

The **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use** (ICH) is a project that brings together the regulatory authorities of [Europe](#), [Japan](#) and the [United States](#) and experts from the [pharmaceutical industry](#) in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

The purpose of ICH is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration.

Harmonisation would lead to a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.

ICH guidelines have been adopted as law in several countries, but are only used as guidance for the [U.S. Food and Drug Administration](#).^[1]

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[\[edit\]](#) History

In the 1980s, what is today the [European Union](#) began harmonising regulatory requirements. In 1989, Europe, Japan, and the United States began creating plans for harmonisation; ICH was created in April 1990 at a meeting in [Brussels](#).

[\[edit\]](#) Structure

Seven parties that represent the regulatory bodies and the research-based industries of the founding members are responsible for the decision making process: the [European Commission](#), the [European Medicines Agency](#) (EMA), the [European Federation of Pharmaceutical Industries and Associations](#) (EFPIA), the [Ministry of Health, Labour and Welfare](#), the 1986 [Japan Pharmaceutical Manufacturers Association](#) (JPMA), the [Food and Drug Administration](#) (FDA), and the [Pharmaceutical Research and Manufacturers of America](#) (PhRMA)^{[\[citation needed\]](#)}.

[\[edit\]](#) Process

The ICH process consists of five steps:

Step 1: Expert Working Group consensus building

When the [Steering Committee](#) (SC) adopts a concept paper as a new topic, the process of consensus building begins. A [rapporteur](#) is usually designated from the industry members of the respective six-member [Expert Working Group](#) (EWG). This EWG consists of regulatory and industry parties (one voting member of each party and region), and observers. The rapporteur prepares an initial draft of the [guideline](#), based on the objectives set out in the concept paper, and in consultation with experts designated to the EWG. The initial draft and successive revisions are circulated for comments within the EWG. Usually, the EWG consultation is carried out by correspondence. Face-to-face meetings of the EWG will normally only take place during the biannual SC meetings. Interim reports are made at each meeting of the SC. If consensus is reached the EWG will sign the *Step 2 Experts Signoff* sheet and submit it to the SC to request adoption. If there is no agreement in the EWG within the time frame the SC may extend the time frame, suspend or abandon the harmonization project.

Step 2: Confirmation of EWG consensus by the SC

Step 2 is reached when the SC agrees, based on the report of the EWG, that there is sufficient

scientific consensus on the technical issues for the draft guideline. This text is signed off by the SC as *Step 2 Final Document*.

Step 3: Regulatory consultation and discussion

The draft becomes subject of consultation in the three regions. It is published in the European Union (as draft [CHMP](#) or [CVMP](#) guideline), Japan (after translation by [MHLW](#)), and the USA (as draft guideline in the [Federal Register](#)) and everybody within these regions can comment on it. There is also an opportunity for companies, associations and authorities in non-ICH regions to comment on the draft, which is distributed by [IFPMA](#) and [WHO](#). After obtaining all consultation results, the EWG will be resumed. A new rapporteur will be appointed from the regulatory party, preferably from the same region as the previous rapporteur. The same procedure described in Step 1 is used to address the consultation results into the *Step 2 Final Document*. The draft document to be generated as a result of the Step 3 phase is called [Step 4 Experts Document](#). If industry and regulatory EWG members agree on the alterations as a result of the consultation, the Step 4 Experts Document is signed by the EWG regulatory experts only (*Step 4 Experts Signoff*) and submitted to the SC to request adoption as Step 4 of the ICH process. If there is no agreement in the EWG within the time frame the SC may extend the time frame, abandon the current draft and resume the process from Step 1, suspend or abandon the harmonization project.

Step 4: Adoption of an ICH harmonised tripartite guideline

Step 4 is reached when the SC agrees that there is sufficient scientific consensus on the technical issues. If one industry party has strong objections to the adoption of the guideline due to deviations of the revised draft from the original consensus the regulatory parties may agree that a revised document should be submitted for further consultation. In this case, the EWG discussion may be resumed. The Step 4 Final Document is signed off by the SC signatories for the regulatory parties of ICH as an [ICH Harmonised Tripartite Guideline](#).

Step 5: Implementation

The ICH Harmonised Tripartite Guideline moves immediately to the final step of the process that is the regulatory implementation. This step is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the [European Union](#), Japan, and the United States. Information on the regulatory action taken and implementation dates are reported back to the SC and published by the ICH Secretariat on the ICH website.

APPENDIX E WEB SITE REFERENCES FOR CLINICAL TRIAL REGULATIONS
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ICH-GCP

Clinical studies should be carried out according to International Conference on Harmonisation (ICH) / WHO Good Clinical Practice standards. This provides a unified standard for the European Union (EU), Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organisation (WHO). Thus, any country that adopts this guideline technically follows this same standard.

I have gathered some links which you may find useful if you plan to do clinical research.

[International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use \(ICH\)](#)

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. This Mission is embodied in the Terms of Reference of ICH.

You will find the latest guidelines at this site.

[The European Agency for the Evaluation of Medicinal Products \(EMA\)](#)

The main task of the EMA is to

- Provide the Member States and the Community institutions with the best possible scientific advice on questions concerning quality, safety and efficacy of medicinal products for human and veterinary use.



- Establish a multinational scientific expertise through the mobilisation of existing national resources in order to achieve a single evaluation via a centralised or decentralised marketing authorisation system.
- Organise speedy, transparent and efficient procedures for the authorisation, surveillance and, where appropriate, withdrawal of products in the European Union.
- Advise companies on the conduct of pharmaceutical research.
- Reinforce the supervision of existing medicinal products in coordinating national pharmacovigilance and inspection activities.
- Create the necessary databases and telecommunication facilities to promote a more rational drug use.

[FDA Center for Drug Evaluation and Research \(CDER\)](#)

The mission of FDA's Center for Drug Evaluation and Research is to assure that safe and effective drugs are available to the American people. The information below provides an understanding of how CDER works to accomplish this mission as it relates to new drug development and review. [See the CDER Handbook.](#)

- [New Drug Development Process-](#) An interactive chart that provides an overview of the new drug development process, with an emphasis on preclinical research and clinical studies conducted by the drug's sponsor.
- [Investigational New Drug \(IND\) Review Process-](#) An interactive chart that provides an overview of CDER's investigational new drug application process, including how CDER determines if the product is suitable for use in clinical trials.
- [New Drug Application \(NDA\) Review Process-](#) An interactive chart that provides an overview of CDER's new drug application review process, including how CDER determines the benefit:risk profile of a drug product prior to approval for marketing.

The section on [regulatory guidelines](#) is worth paying a visit.

[Human Subject Protections- Office of Human Subjects Research, NIH \(OHSR\)](#)


OHSR operates within the Office of the Deputy Director for Intramural Research (DDIR), National Institutes of Health (NIH). The NIH is part of the U.S. Public Health Service (PHS) which is, in turn, an agency within the Department of Health and Human Services (DHHS). The OHSR was established to help IRP investigators understand and comply with the ethical guidelines and regulatory requirements for research involving human subjects. OHSR's overall goal is to promote and support the IRP's efforts to conduct innovative research which protects the rights and promotes the welfare of human subjects. Have a look at the following sites.

- [Guidelines for the Conduct of Research Involving Human Subjects](#)
- [Belmont Report](#)

- [Nuremberg Code](#)
- [The Declaration of Helsinki- Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects](#)
- Department of Health and Human Services (DHHS) regulations for the protection of human subjects, [45 CFR 46](#)

[WORLD MEDICAL ASSOCIATION](#)

DECLARATION OF HELSINKI - [52nd WMA General Assembly, Edinburgh, Scotland,](#)

[October 2000](#) see  (22 Kb)

[Standard operating procedures for clinical investigators](#) (WHO GCP SOP)

This document sets out the objectives of Standard Operating Procedures and defines the Investigators' responsibilities when undertaking a clinical study supported by TDR. It provides instructions for planning, performing, documenting and reporting clinical studies, and also provides a useful glossary of terms.

**APPENDIX F
COMMITTEE ON HUMAN RESEARCH**

SUBMITTING FOR COMMITTEE ON HUMAN RESEARCH (CHR) APPROVAL

Determining Whether CHR Review is Required

The first step in the CHR application process is to determine whether a study requires CHR review:

- If the study is being performed by UCSF faculty, staff, or students (neither the site of the study nor the source of funding, or if there is no funding, matters) **and**
- If the study involves living humans (including studying human biological specimens, medical records and/or other private information; definition is not limited to interactions or interventions with humans) **and**
- If the project is research (a systematic investigation designed to contribute to generalizable knowledge, i.e., will be shared outside UCSF or published)

then the study requires CHR review. Before initiating, modifying, or extending any research project involving human subjects, principal investigators (PIs) must submit an application to the CHR for review and approval. Re-approval is necessary at least annually. No activity, including patient follow-up or data analysis, is allowed to continue if approval has expired. Additional information is available at <http://www.research.ucsf.edu/chr/Apply/chrHowApply.asp>.

Determining the Type of CHR Review Required

The next step is to identify the appropriate application type, that is, Exempt, Expedited or Full Committee. The appropriate type of application reflects the level of risk to the subject. The risk level is compared to “minimal risk” as defined by the federal regulations:

Minimal risk is the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45.CFR.46.102(i)).

If you cannot determine or are unsure about which type of review is needed, please call the CHR Analyst of the Day at (415) 476-1814. A full description of the different requirements is available at <http://www.research.ucsf.edu/chr/Apply/chrHowApply.asp>.

Full Committee Review is required for all studies involving greater than minimal risk. Examples include randomized studies, phase I, II, III and IV trials, studies using investigational drugs and/or devices, and some behavioral interventions.

Expedited Review is appropriate when studies involve no greater than minimal risk and fit into one of nine specific categories, as defined by the federal government. Examples include blood sampling by finger stick, heel stick, ear stick, or venipuncture from healthy individuals, collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, and low risk behavioral research.

Exempt Certification may be allowed if the research involves the lowest level of risk and if it fits into one of four federally defined categories, for example, research conducted in established or commonly accepted educational settings, and the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Emergency Use of an Investigational Drug or Device may be approved in very limited circumstances under very specific conditions. The conditions are the following:

- A life-threatening situation,
- In which no standard acceptable treatment is available, **and**
- In which there is not sufficient time to obtain IRB approval (21 CFR 56.102.d)

Specific information is required before the Chair can sign off on this type of study. Emergency Use should not be confused with “Compassionate Use.” The latter requires review by the full committee.

If you have questions or need additional information, please call the CHR Front Desk at (415) 476-1814.

All submissions are reviewed for completeness by the CHR staff before distribution to the Committee members. Submissions must meet all requirements (e.g., forms completed, consent forms and all attachments included), or they may be returned to the investigator for correction or completion prior to Committee review.

Application Guidelines

The individual listed as the Principal Investigator (PI) for the project must be a UCSF faculty member who meets the eligibility requirements for PI status on grant applications. For studies conducted under the auspices of an affiliated institution (e.g., SFVAMC, UCSF-Fresno, SFDPH) the individual listed as the PI must meet eligibility criteria defined by that institution.

All CHR application forms require the signature of the PI of the study.

All key personnel involved in the conduct of the study should be listed, either on the CHR Cover Page or within the protocol. This is especially important if a grant application for the work is being submitted under a different name from that of the PI listed on the protocol, since there must be a cross-reference. Also, if a study is being done wholly at the Veterans Affairs Medical Center (VAMC), San Francisco General Hospital (SFGH), or Mount Zion (MZ), a VAMC, SFGH or MZ physician or otherwise qualified person must be listed on the CHR Cover Page as an investigator.

Tips to Speeding Up Approval and Preventing Problems

- Remember that chart reviews, studies of specimens (even anonymous ones), and use of information about humans from clinical or research databases all require CHR review or formal exemption.
- Do not change your study procedures or documents without prior CHR approval (unless you had to do so for an emergency situation, in which you must notify the CHR as soon as possible).
- Be sure that your protocol and consent form clearly explain how what happens to subjects in the study will be different from what happens to people who decline participation.
- All documents and sections of the application should be consistent; in particular check the purpose, significance, procedures, benefits, and alternatives in both the protocol and the consent form; use the same name for the drugs throughout the protocol and consent form.
- Use non-technical, everyday language in the consent form. Avoid all jargon.
- Do not use acronyms in either the protocol or the consent form without first explaining them.
- Keep track of the approval expiration date and submit your renewal application in time to receive a new approval before the study expires. Allow four to six weeks.
- Get separate CHR approval for each discrete study. Do not group related studies into a complicated application. You may have several CHR applications for a single grant.

If you have an emergency situation or an unanticipated urgent deadline, please contact the CHR office at (415) 476-1814.

APPENDIX G CRC POST-AWARD RESPONSIBILITIES

The CRC post-award responsibilities, in chronological order, are obtaining the discounted research patient care rates, setting up the clinical trial accounts, registering the trial for an NCT number, registering and linking research subjects to the trial, ordering tests and procedures, and reviewing the Medical Center bill of service and patient visits for accuracy. The details of each duty are explained below.

I. Obtaining the Discounted Research Patient Care Rates

When outpatient visits and inpatient stays are fully or partially funded through research grants or contracts, the Principal Investigator (PI) is responsible for getting the necessary approvals from the Committee on Human Subjects and the Office of Sponsored Research (OSR). The OSR is responsible for submitting the grant application or negotiating the contract with the sponsor.

The Medical Center offers a discount for patient care services on grants, contracts, fellowships, cooperative agreements, and flow-through subcontracts that are provided and billed by UCSF Medical Center at either Parnassus or Mount Zion. The discount is stipulated in the Research Patient Care Rate Agreement negotiated each year with the Department of Health and Human Services (DHHS) Region IX.

A new Research Patient Care Rate Agreement has been negotiated with the DHHS Region IX for patient care charges at the UCSF Medical Center. The new rates are effective May 1, 2004 until amended and are applicable to all patient care services on grants, contracts, fellowships, cooperative agreements, and flow-through subcontracts which are provided and billed by the UCSF Medical Center at either Parnassus or Mount Zion.

In the past, the Medical Center has used the DHHS rate agreement only for federal awards. Effective July 2004, the rate agreement and its associated discounts will now be used for all awards received at UCSF where Medical Center patient care services are incurred, including private industry and non-profit awards.

To obtain the discounted research patient care rates:

- Contact the clinical department(s) that will provide the services included in the study to determine the CDM number and the description for each service. Complete a UCSF Medical Center Research Pricing Request form and send it to Nina Feero at Nina.Feero@ucsfmedctr.org to request research pricing.
- Nina Feero will identify hospital charges for the services, apply the research discount percentages, and return the form with pricing to you.
- If you need to price professional fees (non-investigators), advise Nina Feero of the CPT codes and she will forward you pricing.
- Rates change every year and budgets for multi-year studies must include a yearly cost inflator.

II. Setting Up the Clinical Trial Accounts

To set up the Clinical Trial Account:

- 1) Complete the Clinical Research Study ZZ Medical Record/Visit Number Creation Request form (Appendix i). All study patients must be linked to a ZZ number in IDX.
- 2) Fax or mail the Clinical Research Study ZZ Medical Record/Visit Number Creation Request form to Patient Registration.
 - a) Patient Registration will return the completed form to you along with the ZZ Medical Record number and Visit number.
 - b) The ZZ Medical Record/Visit number will be used on your requisitions for research related procedures and link to each patient recruited in the study.
 - c) The use of this account number indicates that the charges are research related.
- 3) Send the list of new research patients monthly to Nina Feero at Nina.Feero@ucsfmedctr.org.

III. Registering Research Subjects for Inpatient Services

To register Research Subjects for inpatient services:

- 1) Complete the New Patient Registration for Clinical Trial Form (Appendix ii).
- 2) Complete the Patient Reservation Form – Part A (Appendix iii).
- 3) If you need to bill the research study **and** the patient's insurance, complete the Patient Reservation Form – Part B (Appendix iv). The patient's **primary insurance is always billed first** even when a research study is involved.
 - a) For Medicare patients, you must use the Q1 modifier on the encounter form to comply with CMS guidelines.
- 4) If the patient becomes a study patient after being admitted to the hospital, notify admitting to identify the person as a study patient.
- 5) The patient must fill out the study Consent Form.
- 6) Send a copy of the Consent Form to Medical Records to be filed in the patient's Medical Records file. Write the MRN on the top of the Consent Form.
- 7) The Study Coordinator links the patient to the study account using the registration process. This identifies the patient as a study patient.
- 8) Fax required forms to Pre-Admission.
- 9) If the bill needs to go to both the study and the private insurance after the research patient's discharge:
 - a) Accounts Receivable generates a bill and forwards it to the study billing contact person indicated on Patient Reservation Form – Part B.
 - b) The study billing contact returns the edited bill to the Accounts Receivable contact person (within 7 days of receipt).
 - c) **All bills not returned to Accounts Receivable within 7 business days** are charged entirely to the Research Account.
 - d) Room charges, supplies, and recovery time cannot be routed to a research account.
- 10) Update the Patient Enrollment Form (Appendix v) to ensure invoices will be sent to the agencies.

IV. Ordering Tests and Procedures for Outpatient Studies

To order tests and procedures:

- 1) Complete the Label Requisition Form – Clinical Trial Subjects (Appendix vi) to obtain your labels from the registration person in your department.

- 2) Review the medical record to determine the tests or procedures that should be billed to the study.
- 3) Attach the labels to the patient's encounter forms and ancillary service requisitions. Details on completing the patient's label are below.
- 4) If you are unable to create an ancillary visit for a research patient you must send the patient to the Outpatient Registration Department. The Outpatient Registration Department creates required ancillary visits.
- 5) All unused labels should be destroyed once the Clinical Trial Account closes.

Completing the Patient's Label for Outpatient Studies

To complete the patient's label, refer to the chart and examples below.

Data Field	Instruction
Patient's Name	Label contains the patient's name. Leave the label as is.
Patient's MRN	Label contains the patient's medical record number. Leave the label as is.
ZZ MRN	Enter the ZZ Medical Record Number that you obtained from Central Registration.
ZZ Visit Number	Enter the ZZ Visit Number that you obtained from Central Registration. This data field must be updated on a yearly basis.
Study Name	Enter the study name onto the patient's Requisition or Encounter Form.
Date of Service	If the date of service is incorrect, cross it out and write in the actual date of service.

For the portion of the patient's services or procedures that are to be **charged to the research account (study)**, attach a label to a **separate** encounter form or ancillary service requisition, then:

- 1) Cross out the patient's pre-printed visit number.
- 2) If the date of service is incorrect, cross it out and enter the correct date of service.
- 3) Enter the study name.
- 4) Enter the ZZ Medical Record number and ZZ Visit number.
- 5) Cross off the insurance information.

Example 1: A portion of the charges are billed to the insurance company or patient.

NAME:	HIGGINS, HENRY J		
MRN:	11211817	VISIT:	2449571
DOB:	10/11/1925	DOS:	10/29/04 11/01/04
SEX:	M	REF MD:	54251
ATTG MD:		DAVIS, JOHN C MD	
FSC: 302	PLAN:	COPAY: \$10.00	MEDICARE A&B XAB
			ZZ Orien-Rad Study
			ZZ MRN # 10293847
			ZZ Visit # 245678

Example 2: A portion of the charges are billed to the research account (study).

NAME:	HIGGINS, HENRY J	
MRN:	11211817	VISIT: 2449574
DOB:	10/11/1925	DOS: 10/29/04 11/01/04
SEX:	M	REF MD: 54251
ATTG MD:		DAVIS, JOHN C MD
FSC: 302	PLAN:	MEDICARE A&B XAB
		ZZ Orien-Rad Study
		ZZ MRN # 10293847
		ZZ Visit # 245678

V. Reconciling the Medical Center Ledger

The Medical Center Accounts Receivable will generate a ledger (Appendix vii) and forward it to the study billing contact person, which is usually the Clinical Research Coordinator (CRC). The study billing contact person must reconcile the Medical Center ledger against the services and visits that have been provided to patients. If errors are found on the ledger, the study billing contact person must return the edited ledger to the Accounts Receivable contact person within 7 business days. **All ledgers not returned to Accounts Receivable within 7 business days** are charged entirely to the Research Account. After reviewing and reconciling the Medical Center ledger for accuracy, the reviewer must initial and date the ledger.

VI. Deactivating the ZZ Medical Record Number

To ensure that unrelated charges are not charged to a Research Account after the clinical trial is closed, the ZZ Medical Record Number must be deactivated.

To deactivate the ZZ Medical Record Number:

- 1) Contact Tim Arnold by phone at (415) 353-3885 or e-mail at tim.arnold@ucsfmedctr.org.
- 2) Provide Tim Arnold with the ZZ Medical Record Number and request to deactivate the account so that no further charges can be posted after a specific date.
- 3) Destroy all unused labels and forms with the deactivated ZZ Medical Record Number.

APPENDIX H LIST OF CONTACT NUMBERS AND RESOURCES

Department of Medicine

Suzanne Sutton, Director of Research Administration
ssutton@medicine.ucsf.edu (415) 502-4896

Beth Davis, Clinical Research Manager, Div. of Hematology/Oncology
bdavis@medicine.ucsf.edu (415) 353-9674

Joseph Wilson, Assistant Director of Research Administration
jwilson@medicine.ucsf.edu (415) 514-1120

Industry Contracts, Office of Sponsored Research

Erik Lium, Ph.D., Director
erik.lium@ucsf.edu (415) 353-4441

Jim Kiriakis, Manager
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Evelyne Anderson, Assistant
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Tiffany Dao, Assistant
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Kent Iwamiya , Officer
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Jill Lezama, Office Manager
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Mora Mattingly, Officer
mora.mattingly@ucsf.edu (415) 353-4695

Committee on Human Research

John Heldens, Director, HRPP
john.heldens@ucsf.edu (415) 476-9840

Richard M. Wagner, Assoc. Director
richard.wagner@ucsf.edu (415) 476-1172

Lisa Voss, Assoc. Director QA
lisa.voss@ucsf.edu (415) 514-2152

Medical Center Billing

Stanley Warren, Research Billing Training
stanley.warren@ucsfmedctr.org

(415) 353-9256

Tim Arnold, Billing Issues
tim.arnold@ucsfmedctr.org

(415) 353-3885

Derek Howes, Billing Issues
derek.howes@ucsfmedctr.org

(415) 353-3716

Liza Shapiro, Set-up ZZ Research Accounts
liza.shapiro@ucsfmedctr.org

(415) 353-7617

RESOURCES

The Medical Center provides a complementary course on Research Billing Training. To register, please go to <http://training.ucsfmedicalcenter.org>.

The Department of Medicine Research Administration website has resources for forms and procedures located at http://medicine.ucsf.edu/research/new_Training/ClinicalResearch.htm.