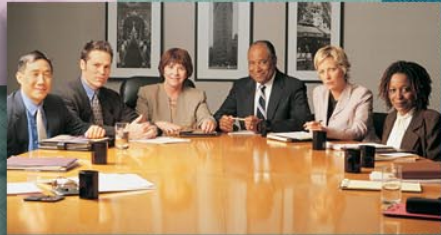




From Paper to People: After IRB Approval of Research Studies



This guide has been prepared for the U.S. Department of Energy (USDOE) Human Research Subjects Program, Dr. Susan L. Rose, Program Manager. Comments may be directed to USDOE, Human Subjects Protection Program, Office of Biological and Environmental Research, SC-72/GTN Building, 1000 Independence Ave., SW, Washington, DC 20585-1290. The DOE Human Subjects website can be accessed at <http://www.science.doe.gov/ober/humsubj/index.html>

From Paper to People: After IRB Approval of Research Studies demonstrates the continuing, collaborative role and the responsibility of an Institutional Review Board (IRB) in working with principal investigators, sponsors, study subjects, the community, and others to promote ethical research. It also emphasizes the interactive and dynamic nature of the review process in contrast to the widely-held misperception that such a review is just a perfunctory response to regulatory requirements.

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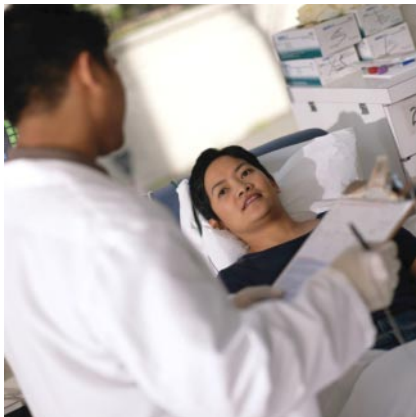
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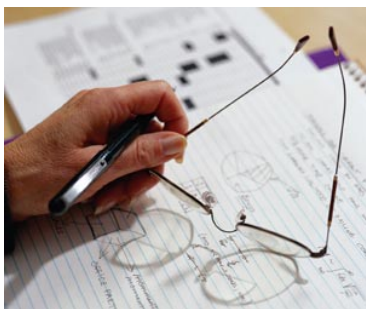
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Introduction

This guide provides an overview of both novel and routine ways to assist Institutional Review Boards (IRB) in assuring that human subject studies, once approved, are conducted properly and follow accepted ethical principles. It is intended as a supplement to human subject protection requirements and not in lieu of the regulations.

The “Common Rule for the Protection of Human Subjects in Research” (Code of Federal Regulations, 45CFR46 Subpart A), a regulation that has been adopted by 17 federal departments and agencies¹, defines the minimum standards and processes that researchers and research institutions must follow to safeguard human subjects. One such requirement is that all human subject research bound by the Common Rule must be reviewed and approved by an IRB before any data collection or research can begin.



The IRB first reviews and then, if acceptable, approves what is here referred to as a “paper study” or “study plan.” The investigator’s actual research and interaction with human subjects begins only after this approval has been obtained. Once the research project is actually undertaken, the IRB shares an ethical obligation with other parts of the Human Subject Protection Program (HSPP) to provide ongoing oversight during the conduct of the research to assure that it is performed in accordance with the protocol as approved. Such monitoring can and should

¹The *Federal Policy for the Protection of Human Subjects* (the “Common Rule”) was adopted in 1991 by 15 Federal departments and agencies and was published at 56 CFR 28002-28032 (1991) and subsequently adopted by the Social Security Administration by Statute and the Central Intelligence Agency by Executive Order.

go beyond the Common Rule's narrowly focused regulatory requirements and does not necessarily end when the protocol is completed. Monitoring also provides the IRB, researchers, administrators, and others an excellent opportunity to enhance the process of human subject protection.

The following topical areas, generally listed in alphabetical order, outline some ways in which the IRB can or should meet its continuing ethical and regulatory responsibilities for IRB approved studies:



Coercion, Inducement, Incentives, and Bonuses Assessment

In the course of continuing review or other oversight review (whether paper review or on-site) the IRB should reexamine the desired vs. actual subject demographics. Such assessment reevaluates the strategies initially used to recruit subjects to determine if they have unintended consequences, if they were coercive, or if they resulted in undue inducement. (Over-recruitment of minorities, workers, or indigent groups through

overly-enticing monetary incentives, job coercion, or health care offers are examples.) The reasons given by the study dropouts and the reasons given by those who declined to participate should be considered as well in the re-evaluation. Thoughtful reflections are needed to evaluate subtle actions that may have influenced justice and equity in enrolling the study population and may thus be avoided for the remaining subjects.

Communication Considerations Among IRBs

For multi-center studies, an IRB may choose to communicate informally with other reviewing IRBs to determine their assessment of initial risks and benefits, continuing review schedules, reporting requirements, etc. Such communication

is an important informational tool and can provide added confidence and insights that all risks and subtle issues have been addressed. Because IRB members have different strengths, experience, perceptions, and perspectives, communication among them can be an asset to the research.



Continuing Contact Schedule (IRB and Researcher)

Options are available to IRBs when there is concern over subject autonomy, subject comprehension, investigator competence, sensitivity, the level of risk, or cutting-edge research. Such options include recommending: pilot testing; reducing the number of subjects until risk is better defined; requiring



IRB reviews more often than annually; or breaking up the protocol into staged tasks. After results are available on the pilot or feasibility research, the IRB can then reassess risk and determine the number of subjects to be allowed and/or the next date for IRB submission and review. This process allows flexibility for the researcher and provides valuable information in a timely manner to the IRB. This better

protects and limits the number of human subjects at risk until that risk is better defined. Additionally, these IRB constraints on a project serve to balance sponsor or researcher enthusiasm for initially enrolling large numbers to answer research questions quickly.

Continuing Review Options

Federal regulations require that all human subject research be reviewed on a recurring basis (“continuing review”) during the life of the study.² The frequency of review depends on the level of risk but should occur at least annually. Listed below are a variety of ways to perform continuing review of a protocol. Whichever methods are used, it is important that the principal investigator (PI) report to the IRB on the study status annually (or sooner) and include required information on significant human subject protection and accrual issues.

- **Paper review.** The IRB, or designated IRB member(s) in the case of expedited review, reviews the continuing review information submitted by the PI. Typically, this information follows the format requested by the IRB and includes summary statistics on subject enrollment and withdrawal, adverse events, protocol amendments, new findings relevant to subject safety, current or modified or proposed informed consent documents, and recent publications of relevance by the PI or others. This review is a regulatory requirement.

²“Guidance on Continuing Review,” Office for Human Research Protections, Department of Health and Human Services, July 11, 2002.

- **On-site review.** Some IRBs conduct on-site human subject research reviews that may be performed by IRB members, agents of the IRB or institution, or research-related committees. These reviews may involve observing subject recruitment, the consent process, data collection, encoding and storage, etc. (see “Support Staff” section). Special care should be taken to choose experienced on-site reviewers to ensure credibility and confidentiality of the review process.
 - **Consent monitoring.** When using a short consent form and a verbal informed consent, the presence of someone (a “consent witness”) who is not part of the research study is a regulatory requirement. However, some IRBs’ policy may allow for observation of the consent process for *any* research (a “consent monitor”). For research of a sensitive nature, an observer of the informed consent process may not be appropriate. Yet, consent monitoring may alleviate concerns about misinformation or coercion and can also serve as a team-teaching and team-building method.
 - **PI/Staff interviews.** IRB-related reviewers or monitors may conduct individual interviews or information sessions with the PI and research staff to observe how the protocol is being put into practice. This permits an ongoing, open dialogue between the IRB and the investigator to help assure the implementation of the protocol as approved.
 - **Subject interviews.** (See also “Research Intermediary” section.) At the discretion of the IRB, interviews with subjects can be requested. These interviews typically occur after the informed consent has been obtained but, if possible, before research has begun. Interviews may also continue during the research. These interviews can bring out participation difficulties, recruitment issues, or reflect cultural concerns. It is especially important that the interviewer has the necessary training and language to talk to the subjects and elicit concerns.
- **PI presentation.** Some IRBs invite the PI to report on the progress of the research at the convened meeting. This meeting allows face-to-face discussion of human subject protection issues related to the ongoing study; fosters free exchange of information, background, and concerns; and avoids misconceptions and delays due to written communication only.



Education

The most important component of any human subjects' protection program is the education of all its participants: the research institution, IRB members, the PI and research staff, the potential subject population, and the local community. Education is an ongoing process that needs to include training in ethics and responsible conduct of research. Education establishes the goal for human subject research conduct, ensuring that the

participants' protection is primary. The initial educational process should take place before participation in the HSPP or before the research process is allowed. *It is equally important that such education be ongoing institutionally and continuing as well as when issues arise among the research team or emanating from the subjects.*

• Participants in the Human Subjects Protection Program (HSPP)

- **Research Institution.** All institutional staff need a basic introduction to the principles of ethical human subjects research and the responsibilities of the IRB. Institutional officials need a basic regulatory and ethical background on human subject research. They must understand that human subject research is being carried out under their authority, that there are associated legal obligations, and that they bear responsibility for promoting a culture at the institution that puts the subjects' protection above the research enterprise. They must also understand that it is their obligation to provide the necessary administrative, personnel, financial, and organizational resources to support the HSPP, and thus the research enterprise at their institution.
- **IRB and IRB Staff.** All IRB members need initial and continuing education on human subject regulations, ethics, and science, as well as the IRB policies and procedures. Some IRBs provide a mentor to new IRB members or allow them to observe an IRB meeting prior to participation.
- **PI and Research Staff.** Researchers and research staff need both initial and continuing human subject education to ensure that the well-being of their subjects remains their primary responsibility and concern. While scientific training is expected, all staff members need additional training in basic ethics and human subject research regulations.
- **IRB and Researchers.** While education enhances the understanding of human subject research, it also can help

improve the working relationship between the researchers and staff and the IRB members and IRB administrator. Both IRB staff and researchers need to approach interactions with respect, collegiality, and open-mindedness.

- **Local Community.** (See also “Outreach Programs” section.) The local community may include potential subjects, local residents, or diverse ethnic groups that need education about what research is being conducted at the institution and the possible benefits and risks of participating in human subject research. Subjects already participating in the research often volunteer as trainers to share their experiences with others and prove to be very effective communicators and educators.
- **Potential Research Subjects.** Education of potential subjects must include information about the research and other available treatment or diagnostic options. Subjects must also be provided with an understanding of their rights and responsibilities as research subjects and an explanation of how they were selected or identified.
- **Education Methods.** The educational method used is as important as the topics covered. Because learners differ, it is most effective to offer education in a variety of ways: films or videos, research facility tours, instrument demonstration, reading materials, lectures, college course work, professional meetings or workshops, hospital grand rounds, online tutorials and e-mail. Community meetings, health fairs, religious events, and school events work well for community education. Regardless of the method, open discussion should be encouraged and fears, risks, and concerns should be elicited and addressed in all interactions and media.
- **Education Topics.** Education in ethics and responsible conduct of research should be varied so that each session has something new to offer. Inclusion of related topics fosters creative thinking. Suggestions include scientific biomedical or behavioral research breakthroughs, subject interviewing techniques, recruitment schemes, consent process, cultural awareness, genetic susceptibility, radiation, and biohazards. Topics should be directly applicable to the audience or the institution’s research portfolio, using case studies or local relevance as the “hook” for engaging learners.
- **Educational Outreach Programs.** It is important that those individuals most likely to be impacted by the research understand the rationale, the process, and their rights. Regulations or research requiring enrollment of under-served populations necessitate well-designed educational outreach programs. Institutions need to make

an effort to meet with the community at times and in places that are optimal for the community. The goal of outreach is to educate, not to recruit, and should focus on making the community knowledgeable and enlightened about the research enterprise. It must also thoroughly



explain what it means to be a research subject. Community outreach can be a good way to find non-affiliated IRB members, communicate research results back to the community, and gain understanding of the institutions' or researchers' goals.

Investigating Research Conduct

Investigation of concerns brought to the IRB about the conduct of any research in the institution provides a forum for continuing education and continuing review, in addition to any necessary disciplinary action. The IRB has

the responsibility for the initial investigation of human subject research comments or complaints. Subsequent actions and notification of institutional officials must follow regulatory and institutional policies to assure that all legitimate inquiries are fully, but fairly, addressed and that corrective actions are taken to protect the integrity and well-being of subjects as well as researchers.

Institutional Research Day

Institutions should consider establishing an annual research day in which investigators present their work to the institutional community. While the entire research community and the institution benefit, this event provides the IRB members and staff with an opportunity for more in-depth learning about ongoing research across the institution. Additionally, it allows for an opportunity to work with investigators presenting research that may not have been identified properly as human subject research or to identify research likely to use human subjects in the future. A research day also provides a forum to learn about research successes and failures. Similar outreach efforts can be designed to inform and educate the geographic community or human subject community, though goals and format will differ.

International Studies Review

International studies require flexible yet innovative strategies to protect subjects because there are



complex and often conflicting requirements established by the participating countries. These strategies may include collaborative ethics reviews with ministries of health, hospital-based ethics boards, or domestically available contacts from the international performance site. Among difficult issues that must be addressed before beginning the study are: defined benefits to the foreign partner and subjects; coordination and communication among the international review boards; recognition of local cultural mores and traditions; resolution of data access, data privacy, and data management procedures; and other issues complicated by language and distance. Language differences pose an obvious problem, and thus certified language translations should be required. Establishing ethical standards in international studies must occur prior to the onset of research, but it is equally important, though difficult, to verify that such strategies are actually practiced during the conduct of international research. Subjects in international studies must receive the same level of protection as do participants in domestic studies.



IRB Approval as a Prerequisite for Scientific Publication

As a condition of publication, many scientific journals now require authors to provide documentation of IRB review and approval and affirmation that the research has been carried out in

accordance with this approval. This requirement encourages PIs to address the ethical implications of their research in design and implementation stages and blocks publication of human subject research that has escaped IRB review.

IRB Initiated Meetings with Institution-Wide Research Support Staff

This innovative institution-wide approach opens channels of communication in all directions. It is a concept initiated by the IRB in which the IRB sets an agenda, issues invitations, and fosters discussion and subsequent actions and interactions between the IRB and research support staff. The research support staff can also be invited to attend periodic informational meetings with IRB members and/or IRB staff to discuss generic processes and problems that may emerge or have emerged during the conduct of research.



Medical Monitor – Independent Monitoring

Medical monitors are physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. For research involving more than minimal risk and/or where the project carries additional sensitivities,

an independent medical monitor may be requested by the IRB. The medical monitor may obtain consent and must be available or present during the intervention employed. Medical monitors should:

- be independent of the research and funding;
- possess sufficient educational, professional, and medical experience to serve as expected;
- report discrepancies or problems to the IRB and researchers promptly; and
- have the authority to stop a research study in progress, remove individual subjects from a study, or take whatever steps are necessary to protect the safety and well-being of research subjects.

Protocol Changes and Amendments

Any significant changes or amendments (initiated by the PI) to the approved protocol must be reviewed and approved by the IRB. This action provides an opportunity to reassess harm-to-benefit ratio to the subjects and to determine if re-consent or subject notification is required.



Specialized Review Committees

Although thorough evaluation of the research protocol by other specialized committees may occur prior or subsequent to IRB approval, it is necessary to assure that these

evaluation processes are all implemented and that the committees inform each other before and throughout the execution of the research.

Furthermore, the data being generated must be evaluated for risks incurred and to establish the quality and success or failure of the research being performed. Communication by and among review committees offers yet another possibility for IRB contact with the research projects. These committees provide additional and different expertise than may be available on IRBs (e.g., data monitoring, dosimetry, biosafety, radioactive and hazardous waste handling, organ doses, and radiation risk).

- **Data Monitoring Committee/Data Safety Monitoring Board/ Interim Data Safety Committee**

These groups consist of skilled experts independent of the research project who, at stipulated intervals, monitor all accumulated safety data and findings from a study to evaluate observable risks and long- and short-term benefits. They issue reports to the sponsors of the study and the investigators. Such reports should be sent to the IRB for additional discourse and action whenever possible. These committees may be required by the Food and Drug Administration (FDA) or National Institutes of Health (NIH) where research risk so dictates, but often are established by the sponsor who may or may not allow IRB access. In all such clinical studies, the sponsor is required to monitor the overall study and to keep all investigators apprised of serious adverse events (the investigator, in turn, needs to keep the IRB apprised of all unanticipated problems involving risks to subjects). Keeping the IRB informed allows IRBs to act on meaningful information they receive.

- **Institutional Biosafety Committee (IBC)**

Institutions that receive NIH support for research involving recombinant DNA must follow the “NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)”. (Although the “NIH Guidelines” may not be a requirement in all instances, it may be good practice to consider them.) The “NIH Guidelines” require that the institution establish an IBC to review and approve recombinant DNA experiments, including human gene transfer research, according to the criteria laid out in 42CFR73. Further, for human gene transfer research, the IBC must ensure that the investigator has addressed all aspects of Appendix M of the “NIH Guidelines”. This includes submitting the protocol to the NIH Office of Biotechnology Activities for initial assessment and, where warranted, to the NIH Recombinant DNA Advisory Committee (RAC) for public review. The IBC cannot make a final determination about a human gene transfer protocol until the RAC review process has been completed. The IRB and FDA can make their determinations before or after RAC review.

- **Radiation Safety Committee (RSC)**

The RSC must approve all research protocols that involve the external radiation exposure of human subjects to x-rays or radionuclides. (However, note that radiation safety requirements vary from state to state and in some states the RSC review requirement is not limited solely to *external* exposure.) Under certain conditions, research protocols that involve exposure of human subjects to radioactive drugs are reviewed by an RSC and a Radioactive Drug Research Committee (see “Radioactive Drug Research Committee” in

next section). There should be a liaison between the IRB and these committees to ensure effective communication and to share information and concerns in providing comprehensive protection for the subjects, including during the study.

- **Radioactive Drug Research Committee (RDRC)**

The RDRC, in accordance with 21CFR361, is authorized by the Food and Drug Administration (FDA) to review the use of certain experimental radioactive drugs or tracers in human subjects research. The research must be intended to obtain basic information regarding the metabolism of the radiotracer, or to investigate human physiology or biochemistry, and must meet established conservative standards for radiation exposure. (Note: Research involving radioactive drugs already approved by the FDA is not subject to RDRC review.

Research on experimental radioactive drugs intended for immediate therapeutic or diagnostic use is submitted directly to the FDA for an Investigational New Drug (IND) assessment.) RDRC approval is in addition to IRB review, and state law may require additional Radiation Safety Committee (RSC) review (see “Radiation Safety Committee” in previous section). There should be an ongoing liaison between the IRB, the RSC, and the RDRC to ensure effective communication with the goal of providing comprehensive protection for the subjects during the study.

Support Staff



- **Clinical Research Associate (CRA).** The CRA is a position intended to be independent of the research staff in reporting, organizational location, and duties. The CRA ensures that good clinical practices and regulatory requirements are followed by the research team and the institution. The CRA may perform tasks such as tracking adverse or unanticipated events and auditing drug accountability records or other systems.

- **Clinical Protocol Coordinator (CPC).** The CPC is part of the research team and assists the investigators in the correct regulatory implementation of the research, IRB reviews, research documentation, quality assurance, and maintenance and review of all records. The CPC should be vested with the authority to stop the study upon evidence of a hazard to safety or rights of subject.

- **Compliance Monitor (CM).** The CM establishes and maintains a protocol compliance monitoring program including random records review and a focus on a safe subject environment. The CM reports to the institutional official and the IRB. The CM is authorized to take actions necessary for the well-being of human subjects and can stop or interrupt a clinical study upon evidence of hazard to the safety and/or rights of the subjects.
- **Research Subject Advocate (RSA)³.** The RSAs are part of the RSA Network at NIH General Clinical Research Centers. An RSA is responsible for ensuring that IRB-approved monitoring plans are fully implemented, the research is in compliance with the IRB-approved protocol, and serious unanticipated or adverse events are reported in a timely fashion to the IRB and appropriate federal agencies. In addition, the RSA may serve as a source of information for patients or volunteers participating in research studies or be requested to monitor research subjects. The RSA reports directly to an individual in the institution whose authority transcends departmental lines and who receives no financial support (salary) from the research protocol, for example, the dean of a medical school.
- **Student Research Advocate (SRA).** Students may propose studies that require human subject review (e.g., for a thesis). The student's faculty mentor can provide the initial support for thinking through issues of scientific design and ethical considerations, but the student usually needs additional support in navigating the entire IRB process. An SRA can provide such support for the novice researcher not only in preparing the protocol for submittal to the IRB, but for additional consultation related to the IRB process while the study is being implemented, i.e., when protocol modifications, further risk evaluation, or reports are required. Such an SRA, a "student mentor," can be a graduate student who is already well versed in human subject research fundamentals. Additionally, the student mentor is an ally to student researchers having a faculty mentor who might not thoroughly address ethical issues or may not fully understand human subject protections.
- **Subject Intermediary.** The subject intermediary is a person who meets with subjects before research begins, but after they have consented to participate, in order to detect potential subject vulnerabilities and concerns. Vulnerabilities detected during this interview may be the basis for the removal of the subject from the study. Vulnerabilities may involve perceived or real coercion, financial

³ A description of the Research Subject Advocate Program as funded by the National Center for Research Resources (NCRR) of the NIH may be found in the NIH document "Division of Clinical Research," November 2001.

need, inadequate background or ability to understand the risks, etc. The subject intermediary serves as a link between the subject and researcher and can reinforce the subject's rights while adding objectivity and confidence from the IRB perspective. *The subject intermediary position should be supported by the institution and not by the researcher because of the inherent conflict of interest.* Positive and negative feedback made by the subject intermediary to the IRB or to the research team may be used to alter the methodology of the research, recruitment strategies, or improve the informed consent process.

- **Subject Matter Experts/Consultants.** When an IRB receives a proposed study involving an area outside of its expertise, it should seek persons with special knowledge of the subject matter of the research to enhance the knowledge base of the IRB review. These expert persons may include social workers, nurses, research pharmacists, and CRA. These experts (who may be considered for permanent membership on the IRB) open channels of communication for the IRB and should be an available option for IRBs at all times. Such experts may also advise both the PI and the IRB if unique or unanticipated situations arise in the course of the study.

Review and Reporting

- **Five-Year Review.** Some IRBs may allow a limited number of continuing annual reviews for long-term studies and require that, at the end of a five-year review cycle for any project, a new application must be made for IRB review. (Some institutions may elect to select different cycles for re-review.) This requirement permits a reasonable cumulative review of the relatively long-term scientific activity yet mandates a fresh look at the risk and benefits for the participating human subjects, contemporary scientific and ethical standards, new findings, and a rethinking of the protocol.
- **Final Research Report.** A final research report submitted by an investigator to close out a project or close a funding cycle serves as an effective vehicle for IRB education. The report can be used to compare original research concepts and IRB review with the actual cumulative risks, benefits, and outcomes of the research. This comparison contributes to the knowledge base for future IRB discourse and uses hindsight to enhance foresight.



- **Results: Subject Notification and Debriefing.** Those who participate in human subject research voluntarily give of their time and energy as well as incur varying levels of physical, psychological, economic, and social risks in order to advance scientific understanding and possible societal benefits. Thus, subjects may have a strong interest in the results of the research and, wherever possible, should be informed of the outcome (successful or otherwise). Depending on the research subject population and the consent given, results may be provided individually and/or collectively. Collective dissemination can occur through meetings with the PI or in written communications, targeted media releases, or other creative outreach mechanisms.

There are two notable issues regarding informing individuals of their own results:

- (1) Some participants may not wish to know their individual results directly and their wishes must be honored.
- (2) The meaning and validity of some results may be hidden in the ongoing research so only group notification may be appropriate, or research procedures may not provide final, valid, or confirmed information so should not be shared until such information is obtained.

Communication of results include debriefing and notification:

- **Debriefing** is a summary description of the overall findings of the research that should be made available to all participants in recognition of their contribution to the project. Debriefing can occur on either an individual or mass media level and is intended to provide participants with a sense of closure regarding the research experience.
- **Notification** is the confidential and direct communication to individual subject participants of findings that have personal health significance for them (e.g., biomedical or psychological test results). Notification must be conducted on an individual level, either by personal contact or letter, and should provide direction for follow-up actions or referral when indicated. The IRB should review both the general dissemination strategy and specific forms of communication involved in the debriefing and notification of study participants for accuracy, sensitivity, and readability, ideally prior to implementing notification and subsequently if questions arise.

- **Serious and Unanticipated Event Evaluation⁴**

The researcher must notify the IRB of all serious and unanticipated events characterized by the Common Rule as “unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with this policy or requirements or determinations of the IRB.” This notification gives the IRB an opportunity to *reevaluate* harms and risks associated with the study and to amend or modify the study to avoid continuing these occurrences or to amend the informed consent form to advise subjects of new information that may impact on their willingness to participate in the research.

⁴ “Unanticipated event” should not be confused with “adverse event” as used by the FDA in their regulations. “Adverse events” must be reported in FDA regulated research.

The Rest of the Tale – Resources (Seminal Papers)

Establishing a personal framework of ethical values requires education in fundamental and classic bioethical writings. Among these, the following are recommended:

- Angell, M., *The Ethics of Clinical Research in the Third World*, NEJM, 1997; 337(12):847-9.
- Angell, M., *Is Academic Medicine for Sale?*, NEJM 2000; 342:1539-1544.
- Beecher, H.K., *Ethics and Clinical Research*, NEJM, 1966; 274:367-372.
- Emanuel, E.J., Wendler, D., Grady, C., *What Makes Clinical Research Ethical?*, JAMA, 2000; 283:2701-2711.
- Emanuel, E., Miller, F., *The Ethics of Placebo Controlled Trials - A Middle Ground*, NEJM, 2001; 345:915-919.
- Freedman, B., *Equipoise and the Ethics of Clinical Research*, NEJM, 1987; 317:141-145.
- Jonson, A.R., *Do No Harm*, Annals of Internal Medicine, 1978; 88:827-832.
- Lantos, J., *The Inclusion Benefit in Clinical Trials*, Journal of Pediatrics, 1999; 134:130-131.
- Rothman, K.J., Michels, K.B., *The Continuing Unethical Use of Placebo Controls*, NEJM, 1994; 331: 394-398.

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