

Chapter 5: Monitoring Research

Research by its very nature is a trip into the unknown for the subjects as well as for the entire investigator team. While the IRB has some monitoring responsibilities, it is not constituted so as to visit sites, examine data, interact with subjects, or make decisions as to the nature of an adverse event. In fact, IRBs function largely on trust; trust that the investigators will carry out the study according to protocol, trust that the data will be collected carefully, trust that the interests of the subjects will be primary and supercede those of the research, and trust that the investigators' conflicts of interest will not interfere with or bias the study. Research catastrophes have led to the conclusion that trust is not enough. Several kinds of research monitoring have evolved to deal with these issues.

1. Clinical Trial Monitors:

Sponsored clinical trials have monitors who make sure that the primary data are collected and recorded properly. They meet periodically with research coordinators and review their study records. They ensure that the reporting of adverse events is complete. This very useful auditing function serves to promote Good Clinical Practices and to enhance the compulsive collection of data. It is required by the FDA, which does not like to review incomplete studies. These monitors do not relate to the subjects.

2. Data and Safety Monitoring Boards (DSMBs):

In 1998 the NIH wrote policies for Data and Safety Monitoring Boards for studies supported by its Institutes and Centers. The report can be found at: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>

Key elements are replicated here but the entire policy is brief.

It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

Although there are potential benefits to be derived from participation in clinical research, the IRBs and the NIH must ensure, to the extent possible, the safety of study participants and that they do

not incur undue risk and that the risks versus benefits are continually reassessed throughout the study period.

All clinical trials require monitoring -- Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III); etc.

Monitoring should be commensurate with risks -- The method and degree of monitoring needed is related to the degree of risk involved. A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. Risk associated with participation in research must be minimized to the extent practical.

Monitoring should be commensurate with size and complexity. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator or NIH program staff in a small phase I study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

Double blinded randomized trials need intermediate assessment of both efficacy and safety as they progress. DSMBs are now constituted to carry out that function for both commercially sponsored and Federally sponsored clinical research. They are required for therapeutic studies. We expect that DSMB members be expert in the various aspects of a trial and include the capacity for sophisticated statistical analysis. DSMB members should be independent of the research and have no conflicts of interest in relation to the research. DSMB deliberations contain open and closed portions. In the closed portions, the blinding is removed to determine whether one experimental group is experiencing significantly greater efficacy or adverse events than others. DSMB members sign non-disclosure agreements and must maintain the highest degree of confidentiality in regard to their deliberations.

DSMBs have been known to stop trials early either because of established efficacy to the tested agent or increased risks associated with one arm of the trial. Such actions must be taken cautiously and with great care, considering the huge investment made by participants, investigators and sponsors alike. However, the DSMB is hopefully expert and objective in its deliberations. DSMBs have stopped the Women's Health Initiative, the NIDDM diabetes study, and the study of XXXX for breast cancer among others. They constitute a strong force for maintaining the ethical conduct of clinical research and are increasingly utilized. However, DSMBs have no direct contact with research subjects.

3. **Research Subject Advocacy:**

In 2001 the National Center for Research Resources established research subject advocates (RSAs) in all General Clinical Research Centers (GCRCs) funded by the NIH. These individuals were charged to develop a program of monitoring research carried out on the GCRCs, advocating for the subjects, and educating the research team as to their performance and ethical responsibilities. The RSA has access to the research participants, the protocols, DSM reports and the research team. The RSA ensures proper reporting and documentation of adverse events and protocol violations. Considerable information has been generated indicating that research errors are common and that the basis is often ignorance of standards, definitions and rules. The other main source of nonadherence is logistical problems in actually carrying out the research. These unanticipated problems can lead to protocol violations in order to get the research done.

4. **Cancer center review:**

Cancer Centers are provided funds for staff to monitor all the research that is under their auspices. They provided auditing functions as well as scientific and data and safety monitoring review.

5. **Gene Therapy:**

Gene therapy protocols undergo periodic audits and must be approved by the RAC in addition to all standard reviews.

6. **Stem cell research:**

Stem cell research is being monitored both by IRBs and by specially constituted ESCRO (embryonic stem cell research oversight) committees. The research will be carefully monitored and the use of the stem cells audited in detail, to some extent due to societal sensitivity to the abuse of the research material.

Cases Chapter 5

Case: Regulatory Controls and Career Success

Dr. Atkins is finally beginning to enjoy the success of her hard work on angiogenesis factors in cancer biology. Her work on HTGF (hypoxic tumor growth factor) led directly to her discovery of the HTGF receptor for which the active site was easily identified.

She had gone early to the Office of Intellectual property, which got patent protection for HTGF and its receptor as well as the use of its active site. It was suggested that Dr Atkins form a company and license back the rights to develop her discoveries but she decided that she was enjoying her life, did not want further complications and could help a commercial firm develop the therapeutic agent.

A major cancer-oriented biotechnology company Betagen, licensed Dr. Atkins' technology for a considerable sum. Although the company preferred to pay in cash, both the university and Dr. Atkins wanted and received a significant amount of equity, predicting that development of HTGF antagonists will be very profitable.

Betagen then asked Dr. Atkins to be a major consultant to them. Her knowledge was worth \$50,000 a year for monthly one day visits. They could pay her in cash or stock. It was up to her.

After two years of hard work, with Atkins' insights, the appropriate antagonist was synthesized and tested extensively in animals. Phase 1 and 2 trials in HTGF-over expressing lung carcinoma, one of the leading target cancers were completed.

Dr. Atkins is an oncologist specializing in lung cancer. She belongs to the departmental practice plan. She was approached by the contract clinical trials organization handling the HTGF antagonist to be the local PI for the definitive Phase 3 trial. She agreed to participate because she really wanted her patients to experience the benefits of her basic research. She wanted to be a truly translational investigator, so it was arranged.

She presented the research protocol to the IRB and Conflict of Interest Review Committee (CIRC) for approval.

The CIRC is concerned about her multiple roles – inventor, consultant, and PI and feels that there needs to be some accommodation made if the University is to accept the contract. She seeks a solution that will give her patients access to the trial.

The Contract and Grant Officer signs the contract for the University. Dr. Atkins and all her co-investigators also sign the contract indicating that they have read the agreement and will adhere to the terms including the confidentiality statement.

After the appropriate accommodation was made and the conflicts of interest noted in the informed consent document, the study was approved and began.

About 3 months into the 2 year accrual period, Dr Atkins saw a journal advertisement from Betagen offering basic research support for investigators studying cancer growth inhibition. She applied and was awarded \$100,000 annually for 3 years. Again, because of University rules Dr. Atkins had to provide the CIRC with information about her relationship to Betagen. She didn't understand why, since this basic science grant had nothing to do with the clinical trial and so she told her grant administrator to complete a negative disclosure form that she signed and submitted to the Contract and Grant Office with other grant paperwork.

Dr. Atkins was pleased to be called by a large investment group about a year into the study to consult with them about newer treatments for cancer. They would pay

\$2500 per hour for her time on conference calls. She considered this a perquisite of her success and participates about every 3 months.

Meanwhile, Betagen, anticipating the impending success of the trial, asks Dr. Atkins to join their Speakers Bureau to give oncologists a chance to hear her views on cancer therapy. She thought that this would give her greater exposure and prestige so she went to the speakers indoctrination meeting and was put on their list. She received numerous requests to give talks.

She has begun to realize that all these activities are beginning to cut into her family life and her basic research but she loves the recognition and respect.

Questions:

- 1. Dr. Atkins has entered the golden period of her career. Has her success created issues in relation to University rules and regulations?**
- 2. What issues have arisen in terms of her core career as a result of her success?**
- 3. What are her reporting responsibilities to the CIRC?**
- 4. What are her reporting requirements to her department?**
- 5. Do any of her activities put her career at risk?**

Case: Relations to Industry

Super Pharmaceuticals has been conducting a randomized double-blinded study of a revolutionary new treatment for osteoporosis at a major teaching hospital for the past 3 years; Dr. Miller is a major stockholder in the company and has been PI of this project at the hospital. He has 200 women over the age of 65 enrolled and he is enthusiastic about the drug. At the annual stockholders meeting the company disclosed positive findings, making the stock soar.

In a meeting with his Clinical Trials Coordinator Dr. Miller learns that two women in the study have developed a dilational cardiomyopathy. Dr. Miller informs the Data and Safety Monitoring Board, Super Pharmaceuticals and his institution's IRB of the SAE (serious adverse event).

The Data and Safety Monitoring Board reviews the data and reports simply that the study should continue because they believe the cardiomyopathy could not be clearly related to the drug. They send that report to the IRB and FDA. They do not require informing current and future study patients, or amending the protocol or Consent document.

Questions:

- 1. What are the issues in this case?**
- 2. Is the institution at any risk here?**
- 3. What do you believe the response should be to the serious adverse events?**
- 4. How would you feel if Dr. Miller were studying mostly his own patients?**
- 5. Were there any explicit or potential issues that might have affected initial approval of the**

study?

Case: Translational Research

Jones, a translational researcher in metabolism in a major academic department of medicine developed a small molecule PYY derivative that traverses the blood-brain-barrier and activates the satiety center. This anorexigenic agent has safely reduced appetite and weight in genetically obese mice and rats as well as normal animals, which became emaciated. Jones calls the product “Sleek.” Studies in other species demonstrated the unique effectiveness of Sleek.

Jones got Sleek patented by the university and founded a biotech company “ANOREX” to complete the clinical trials and market the product as well as to develop even better agents. Jones became CEO of the company and took an allocation of 25% of the stock. Obtaining venture capital funding was a snap.

Phase 1 and 2 clinical trials on obese patients in Jones’ metabolism clinic did not demonstrate any adverse effects and allowed the establishment of a dosage schedule adequate for a large Phase 3 clinical trial.

ANOREX engaged a clinical trials company to conduct the trial on Jones’ design in consultation with the FDA. Sleek would be given at two doses versus control to 500 individuals at greater than 100% above ideal body weight for 12 weeks in a double-blinded randomized manner. DEXA scans, weights, BP, and many chemistries would be done before beginning and at 1,3,6,9 and 12 weeks. Following completion of the initial trial, all participants would be placed on Sleek in an open label trial for six months. Jones would enroll 100 of the participants from his metabolic clinic to keep an eye on the study and the remainder will be enrolled in 20 cooperating sites.

Since Sleek is a new drug, Jones arranges a Data and Safety Monitoring Board consisting of the leadership of ANOREX and three of the other Principal Investigators, each of whom receives consulting fees from ANOREX.

All the participating IRBs approve the trial.

During the course of the 12-week trial, participants lose an average of two pounds weekly, are never hungry, and are delighted. A participant who works at a local newspaper asks Jones for an interview and he graciously gives an upbeat report in which the interviewer is cautioned that the trial remains in progress and is not conclusive.

During the open label portion of the trial two participants from Jones' metabolic clinic become ill. They develop congestive heart failure and, on hospitalization are found to have dilational cardiomyopathy. Sleek is stopped in both cases and the serious adverse event (SAE) is reported to the IRB and the FDA. However, the report claims that the drug was probably not the cause of the event since there were no reports of trouble at the other sites and idiopathic cardiomyopathy was not all that uncommon. One of the two patients improves rapidly and the other deteriorates to the point of requiring a heart transplant.

Questions:

- 1) Given the information provided, if you were an IRB member what questions would you have had for Jones prior to approval of the protocol?**
- 2) Would you have insisted on any changes to the trial?**
- 3) If you were the IRB chair, reading the SAE report, what further steps would you have insisted on?**
- 4) The Data and Safety Monitoring Board was scheduled to meet semi-annually. Should they have any further involvement in the process and if so what would you, as a member, insist on?**

Bibliography

(2003). "American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research." *Journal of Clinical Oncology* 21(12): 1-10.

Burman, W., R. Reves, et al. (2001). "Breaking the camel's back: multicenter clinical trials and local institutional review boards." *Ann Int Med* 134(2): 152-7.

This article, which has become historical by now described the lack of capacity of currently constituted IRBs to handle the increasing protocol load and also evaluate safety reports from large randomized clinical trials in a timely fashion. The rapidly rising number of multicenter clinical trials had put unprecedented stress on the institutions that was compounded by an increasing number of IRB investigations, often leading to publicly announced closures of major academic institutions' clinical research programs. They proposed a systematic investigation of the entire clinical research review process. This was carried out by the Institute of Medicine.

Cairns JA, Hallstrom A, et al. (2001). "Should all trials have a Data Safety and Monitoring Committee?" *Am Heart J* 141(1): 156-63.

This paper reviews development of DSM boards and explains the rationale for having their oversight. It reviews their functions and activities and ends by proposing a set of standards for appointment and charter of a DSMB.

Drazen, J. M. (2002). "Institutions, Contracts, and Academic Freedom." *N Engl J Med* 347(17): 1362-1363.

This editorial discusses contracting rules for clinical research carried out in academic institutions, focusing on insisting on the freedom to publish results no matter what they reveal.

Friedrich, M. J. (2005). "Neuroscience Becomes Image Conscious as Brain Scans Raise Ethical Issues." *JAMA* 294(7): 781-783.

Gamache, V. (2003). "Increasing Presence of Data Monitoring Committees." *Center Watch* 10(4): 1, 8-11.

This paper reports on the rise of Data and Safety Monitoring Boards as a further mechanism to oversee clinical research. Since then they have become almost ubiquitous.

Russo, E. (2000). "Monitoring Human Subjects and Clinical Trials." *The Scientist*: 6.

This news report indicates that IRBs are inadequate to monitor research even though they were given that mandate.

Slutsky, A. S. and J. V. Lavery (2004). "Data Safety and Monitoring Boards." *N Engl J Med* 350(11): 1143-1147.

(2003). "American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research." *J Clin Oncol* 21(12): 2377-2386.

These are the 2003 American Society of Clinical Oncology rules and proposals for clinical research. These include centralized IRBs, standardized forms, and making informed consent documents more directed at informing about the study. They also promote more institutional support and education in ethical clinical research.

<http://www.jco.org/cgi/content/full/21/12/2377>

Andrews, J. (2006). "Research in the ranks: vulnerable subjects, coercible collaboration, and the hepatitis E vaccine trial in Nepal." *Perspect Biol Med* 49(1): 35-51.

The military are vulnerable subjects because requesting participation in research is, in itself, coercive. The example of the hepatitis E vaccine trial employing the Royal Nepal Army demonstrates the vulnerability of the soldiers.

http://muse.jhu.edu/journals/perspectives_in_biology_and_medicine/v049/49.1andrews.html

Hahn, S., P. R. Williamson, et al. (2002). "Investigation of within-study selective reporting in clinical research: follow-up of applications submitted to a local research ethics committee." *Journal of Evaluation in Clinical Practice* 8(3): 353-359.

By comparing the initial protocol with the results and analysis of a small group of studies in Reading, U.K., the authors found that the primary objective was often not given and the analysis differed from that proposed. These results, if extrapolated, would indicate huge biases in clinical research.

<http://www.blackwell-synergy.com/doi/abs/10.1046/j.1365-2753.2002.00314.x>

Dominguez, R. A., D. J. Feaster, et al. (2005). "Searching for an efficient institutional review board review model: Interrelationship of trainee-investigators, funding, and initial approval." *Journal of Laboratory and Clinical Medicine* 145(2): 65.

These authors studied the IRB review process at their own institution to determine factors leading to delay in approval. They found that the presence of a trainee and the absence of external funding both were associated with delayed approval and suggested an educational intervention.

<http://www.journals.elsevierhealth.com/periodicals/ymlc/article/PIIS002221430400349X/abstract>

Judy Illes, et al. (2004). "Discovery and disclosure of incidental findings in neuroimaging research." *Journal of Magnetic Resonance Imaging* 20(5): 743-747.

This preliminary study identified the serious problem of incidental findings in brain imaging research. The findings may be quite important yet professional reading of the studies may be substantially delayed. Experimental designs should address the importance of a timely review of studies and reporting of coincidental findings.

Fisher, C. and S. Kornetsky (2005). "SACHRP recommendations for review of children's research requiring DHHS secretary's approval." *IRB* 27(3): 8-10.

These recommendations of SACHRAP, the Secretary's Advisory Committee on Human Research Protection, deal with the Federal 46.407 provisions to have control review of protocols that have more than minimal risk in pediatric research subjects.

Jones, A. M. and B. Bamford (2004). "The other face of research governance." *BMJ* 329(7460): 280-281. <http://bmj.bmjournals.com/cgi/content/full/329/7460/280>

Two descriptions of what happened when a protocol deviation was discovered and the research ethics office was notified. Was the response overkill or not?

Bhutta, Z. (2002). "Ethics in international health research: a perspective from the developing world." *Bulletin of the World Health Organization* 80(2): 114-20. [http://www.who.int/bulletin/archives/80\(2\)114.pdf](http://www.who.int/bulletin/archives/80(2)114.pdf)

This is an analysis of international research involving developing countries. He focuses on the elements that require discussion in the developing countries, including "standard of care" and prior agreements. The author also argues for more training in bioethics in developing countries and more focus on the public health measures that will do the most good for the population.

Korenman, S. and L. Shaker-Irwin (2003). Research Subject Advocacy--A New Way to Enhance Integrity in Clinical Research. *Endocrine Society News*. 1: 6-7.

The National Center for Research Resources provided General Clinical Research Centers funding to recruit and hire individuals to be Research Subject Advocates. The job description was somewhat vague. In this paper the authors describe their response to the charge to advocate for subjects and to oversee their research activities in a constructive manner. This describes how UCLA did it up to the date of the paper. This role has continued to evolve to include much more education, protocol monitoring, and face to face relationships with subjects and the research team.

Neill, K. (2003). "Research Subject Advocate: A New Protector of Research Participants." *Accountability in Research* 10(2): 159-74.

In October 2001 General Clinical Research Centers were funded to recruit Research Subject Advocates (RSAs). They rapidly developed their job descriptions in such a way as to help participants in clinical research throughout the experience. This paper describes the early days of the program.

Steinbrook, R. (2002). "Improving Protection for Research Subjects." *N Engl J Med* 346(18): 1425-1430.

A professional examination of the frailties of the clinical research process with attention to IRBs, DSMBs and other vehicles for accountability. This is one of a series of activities in various journals addressing the "crisis" in the process of clinical research identified by the serious failures occurring at Penn, John Hopkins, Rochester and other major research institutions.

Vincent, C. (2003). "Understanding and Responding to Adverse Events." *N Engl J Med* 348(11): 1051-1056.

In this essay the author focuses attention on the process of dealing with serious adverse events both as how to analyze them constructive to improve future performance and to support the participants, their families and the research team under these stressful conditions. He discusses system weaknesses as well as individual errors in the setting not of blame but of fostering improvement. Owning up to problem, truth-telling, and support are very important but prompt and through attentions to harms done is essential to reestablishing confidence in the research team may also be seriously affected by a serious adverse event and should have an opportunity for expression and counseling if appropriate. This paper will really help the team to deal with a serious adverse event.

Marshall, E. (2000). "BIOMEDICAL ETHICS:Penn Report, Agency Heads Home In on Clinical Research." *Science* 288(5471): 1558-1559.

This report describes the response of Penn to the egregious problems in their clinical research activities revealed by the Jesse Gelsinger case. They are planning to use outside monitors for studies in which the institution has an interest. Furthermore their gene therapy institute would no longer do clinical trials. Both Penn and various Federal agencies indicated plans to more monitoring of clinical research.