Human Safety in Clinical Research

Michael J. Schmidt

Recently, a great deal has been written about clinical research involving human subjects. Unfortunately, much of the news has been bad—fraudulent investigators in academia exposed, fined, and sent to prison; institutional review boards (watchdog groups for ethics and safety in research) examined and restrained or shut down by the U.S. government because of inappropriate practices; a physician failing to follow regulatory guidelines and treating cancer subjects with a vaccine manufactured with a “lack of control;” the death of a young man in a university clinical trial testing a gene therapy. The FDA reports that the number of complaints filed against clinical investigators by their own staff members, pharmaceutical sponsors, or FDA investigators markedly increased in 1999.

Reports and recommendations have issued from government agencies. The Office of Inspector General of the U.S. Department of Health and Human Services published a report on recruiting subjects into clinical trials that pointed to some possible reasons for problems and suggested some changes. Editorials have been written. Academia, as represented by a task force on research accountability sponsored by the Association of American Universities, has also investigated and analyzed the current state of clinical research practices. Very clear “conclusions and calls to action” are stated in their report. Some private focus groups, such as PRIM&R (Public Responsibility in Medicine and Research), are coming forth with performance standards, self-assessment tools, and peer-based accreditation of institutional review boards (IRBs) and institutions engaged in human research. Education, testing, and accreditation for clinical research physicians and their staff members are being considered, and new regulations or guidelines for oversight of clinical research seem imminent.

Speaking from the highest level, former Health and Human Services secretary Donna Shalala, PhD, voiced her opinion about recent problems in the execution of clinical research and provided specific recommendations for change, as did former FDA commissioner Jane Henney, MD.

The analyses and recommendations in these reports may lead readers to question whether clinical research is being conducted safely, and to ask how the welfare of human subjects is being maintained. The public literature contains little about the standards and practices in place designed to ensure subject safety and well-being in industry-sponsored trials, although much, in fact, is being done.

With this in mind, this article describes the process of drug discovery and development in the pharmaceutical industry, with special emphasis on the regulations and practices in place to ensure that people who volunteer to participate in clinical research on new drugs are treated with respect and dignity, and that all measures are taken to ensure their safety and well-being. Specifically,

- What is the process of drug discovery, research, and development in the pharmaceutical industry?
- What are the research standards that protect subjects?
- How do pharmaceutical companies ensure that human protection standards are in place and followed?

Core philosophy of drug development

Patient well-being and safety are a constant concern throughout the long (up to 15 years), expensive (perhaps $500 million), detailed (about 400,000 pages in a typical NDA) development process for a new drug. In fact, safety is a powerful business and marketing driving force. The reason is simple and practical: Unsafe or troublesome drugs don’t remain long on the market because they do not serve customers well. As a result, along with finding drugs for untreated medical conditions, improving the safety or side-effect profile of existing drugs is a target of drug discovery scientists.
The drug development process is divided into distinct stages (Figure 1).

- Development of a therapeutic target or concept and experimental animal models of the disease state
- Synthesis or expression of new compounds (referred to as new molecular entities, or NMEs) to affect the disease state
- Efficacy pharmacology studies of the NMEs in cell cultures, isolated organ tissues, or animal models and selection of a “lead candidate” entity
- Safety and toxicology studies in animals
- Phase 1 initial human safety trials, dosing for tolerability in healthy volunteers
- Phase 2 testing of the drug candidate in relatively small numbers of subjects with the target disease, to establish human safety, evidence of efficacy, and effective dosages
- Phase 3 testing of the new therapy in a large number of subjects, often throughout the world, to further accumulate statistical evidence of safety and effectiveness
- Submission of research results to regulatory agencies (FDA, for example) for their review for registration and marketing clearance
- Marketing and sale of the drug, accompanied by postmarketing safety surveillance and reporting
- More Phase 3 studies for new applications and new uses
- Phase 4 studies in the target population to collect more data on safety and efficacy in defined populations.

**Pharmaceutical industry data indicates** that 5 in 5,000 new molecules produced by pharmaceutical companies get to human trials, and only 1 of those 5,000 makes it through all phases of the arduous development process to registration. Then, during their commercial lifetimes, only 3 drugs in 10 provide a positive return on their R&D investments.19

**Glossary**

**IND** Investigational New Drug application, filed with FDA after preclinical testing, for permission to proceed with human tests.

**efficacy pharmacology** Evaluation of a drug’s characteristics, effects, and uses with regard to the target illness, and its interactions with living organisms.

**healthy volunteer** A healthy person who agrees to participate in a clinical trial for reasons other than medical and receives no direct health benefit from participating.

**human subject** An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. (21 CFR 50.3)

**Phase 1** Initial safety trials on a new medicine in which investigators attempt to establish the dose range tolerance for single and multiple doses in about 20–80 healthy volunteers.

**Phase 2** Pilot clinical trials to evaluate efficacy, safety, and therapeutic dose range in selected populations of about 100–300 subjects who have the disease or condition to be treated, diagnosed, or prevented.

**Phase 3** Multicenter studies in populations of perhaps 1000–3000 subjects (or more) for whom the medicine is eventually intended.

**Phase 4** Postmarketing trials to provide additional details about the product’s safety, efficacy, and additional uses.

**preclinical studies** Animal studies that support Phase 1 safety and tolerance studies and must comply with good laboratory practice (GLP). Other preclinical studies are done in discovery research laboratories to support drug efficiency claims.

**subject/trial subject** An individual who participates in a clinical trial, either as recipient of the investigational product(s) or as a control. (ICH) See also healthy volunteer, human subject. (ICH 1.57)

**Discovery research, safety testing**

Basic research scientists working in discovery groups in the drug industry are all intent on finding “a winner.” A winner is a novel and patentable new molecular entity that
- positively affects a disease state.
- improves a patient’s quality of life.
- is safe.

It must be possible for the final product to be manufactured
- at a reasonable cost.
- in a way that is safe for the production workers and the environment.

Achieving all of these “desirables” is a monumental feat. The animal research portion of an IND application must contain a significant amount of information that demonstrates the effectiveness of the drug in animal models that approximate the target disease condition. It must be good enough to justify administering it to humans; the efficacy pharmacology must show significant promise of improved human therapy. Only those drugs with the most promising profiles are selected to move forward in development. Industry scientists design new molecules with safety in mind, eliminating from the start...
certain elements and chemical groups that have been known in the past to produce toxicities in animals or adverse reactions in humans. The goal of these medicinal synthetic organic chemists and molecular biologists is to “design-in” safety, to the degree that knowledge and technology make this possible.

When an NME survives the rigors of early discovery research, researchers run safety tests in animals and in vitro (in test tubes and cell cultures) to detect any major toxicities—for example, irritation to tissues, gross cellular damage, or genetic mutational effects. The tests fulfill the strict safety testing requirements set by international regulatory agencies. The purpose of performing these high-dosage, multidose studies in various species for significant periods of time is to minimize the risk of serious adverse effects occurring in humans during initial single-dose clinical studies. Most new drug candidates fail this exhaustive safety test battery. Thus, before any human being is administered a new drug candidate, many efficacy and safety-focused studies—which accumulate thousands of data points—have already been conducted. Company toxicologists and research physicians scrutinize the results. Then, the sponsor company requests permission from regulatory agencies—which also review the data—to begin human testing.

Regulatory agency staff reviewers include therapeutic-specific pharmacologists, toxicologists, chemists, and physicians. Their principal goals are to determine whether the nonclinical test data provides adequate evidence that the drug is reasonably safe for administration to humans; to determine whether using the protocol for the proposed studies will expose clinical subjects to unnecessary risk (Phase 1), and whether the studies are of sufficient scientific quality to yield the safety and efficacy data required for marketing approval (Phases 2 and 3); and to determine whether the compound is stable and reproducible. The FDA has 30 days to put a drug on clinical hold, pending resolution of its concerns, or the trials may begin.

**Clinical research**

**Phase 1.** Research protocols for Phase 1 (first-in-human) studies are developed and approved by medical staff, toxicologists, and managers in the pharmaceutical company who have reviewed the preclinical toxicology studies. Protocols are then reviewed by an institutional review board (IRB) or ethics committee (EC). Ethical review bodies are located in academic institutions and other clinical testing centers throughout the world. Phase 1 studies are generally carried out in specialized clinics, where the new drug candidate is administered to about 20–80 healthy volunteers, who are paid for their participation in the study. These subjects are closely observed 24 hours a day to record the effects of “first dosing.” Based on the results, dosing is increased until some evidence of an effect on the body is noted. Results can be as subtle as a change in “general feeling” or as specific as a change in heart rate.

In cases where the drug candidate might be inherently toxic or cause genetic damage, but where such side effect possibilities are acceptable because of the life-threatening nature of the target disease—for example, cancer, AIDS—Phase 1 studies are conducted in diseased subjects from the start.

**Phase 2.** The pharmacological effects revealed by Phase 1 studies provide the basis for setting dosing levels for Phase 2 (safety and efficacy) studies, which may involve as many as 100–300 subjects, including people with the target disease or condition. Key objectives for these studies are to establish how well a relevant population tolerates the NME, to document side effects, and to note any beneficial effects of the drug candidate. Establishing an effective dosage and schedule is critical in early Phase 2 (sometimes called Phase 2a) studies. Further safety studies in animals are run in parallel with human dosing, to expand the knowledge base for high-dose and long-duration administration in higher-order species such as dogs and monkeys. Special animal studies are also conducted that focus on the NME’s effects on fertility, reproduction, and fetal development.

Late Phase 2 (often called Phase 2b) research involves many more subjects under the care of physicians at multiple institutions and is designed to begin establishing the drug candidate’s therapeutic effectiveness. The research questions are clear: Is the drug effective? At what dose does benefit occur? What is the duration of its effectiveness? Have new safety-related effects been detected? Do the therapeutic benefits of the drug candidate outweigh the discomfort of any side effects that accompany the drug’s action?

**Phase 3.** This phase of new drug testing is conducted in many clinical sites—often in many nations—and in many people affected by the target disease or condition. Studies of a single drug candidate can involve as many as 10,000 subjects.

**Phase 4, postmarketing surveillance.** Studies of a new drug continue after it is marketed. As more is learned about the effects of the drug, new trials are conducted and new indications are added, which may broaden the applications of the therapy.

**Ethical standards and regulations**

Nations throughout the world have regulations that govern the conduct of clinical

### PRECLINICAL safety testing in animals

<table>
<thead>
<tr>
<th>Safety focus</th>
<th>Test model</th>
<th>Duration of dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate/acute toxicity</td>
<td>Rat, mouse, and dog</td>
<td>1–14 days</td>
</tr>
<tr>
<td>Short-term toxicity</td>
<td>Rat, mouse, and dog or monkey</td>
<td>30–90 days</td>
</tr>
<tr>
<td>Long-term toxicity</td>
<td>Rat, mouse, and dog or monkey</td>
<td>6–12 months</td>
</tr>
<tr>
<td>Carcinogenicity (lifet ime toxicity)</td>
<td>Rat and mouse</td>
<td>24 months</td>
</tr>
<tr>
<td>Carcinogenicity (mechanism of action)</td>
<td>Cell culture/in vitro models</td>
<td>Days</td>
</tr>
<tr>
<td>Teratology/birth defects</td>
<td>Mouse, rat, and rabbit</td>
<td>Months–two generations</td>
</tr>
<tr>
<td>Fertility</td>
<td>In vitro sperm mobility testing</td>
<td>Days</td>
</tr>
<tr>
<td>Fertility and reproductive behavior</td>
<td>Rat and rabbit</td>
<td>Days–months</td>
</tr>
<tr>
<td>Physiology/pharmacology profile</td>
<td>Rat, mouse, and dog</td>
<td>Days</td>
</tr>
<tr>
<td>Absorption-distribution-metabolism-elimination (ADME)</td>
<td>Rat, mouse, and dog or monkey</td>
<td>Days–months</td>
</tr>
</tbody>
</table>
research, and many nations expect researchers to follow specific guidelines, such as the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice. Regulations and guidelines are generally based on the principles of the Nuremberg Convention. The Nuremberg Code was written in 1946 in an effort to prevent a recurrence of the human experimentation atrocities of World War II. This document stated that all research in humans should be done with the well-being of the subject of primary concern.

The 1964 Declaration of Helsinki includes significant detail about clinical trial practices and the rights of potential subjects to be informed about risks, benefits, and alternative therapies.20 It has been amended several times, most recently in 2000. Together, several parts of the U.S. Code of Federal Regulations (21 CFR 50, 21 CFR 54, 21 CFR 56, 21 CFR 312) constitute the good clinical practice (GCP) regulations for studies conducted in the United States. The regulations detail the responsibilities of sponsors, investigators, and IRBs, and also outline monitoring practices to ensure regulatory and study design compliance and subject safety.21 Similarly, the ICH guideline on GCP provides detailed instructions for investigators, institutions, sponsors, and IRBs.

In the 1990s, the International Conference on Harmonisation brought together regulatory agencies and industry representatives from the United States, Europe, and Japan—and observers from all over the world—to agree to a single set of technical requirements for the registration of pharmaceuticals for human use. This process is now nearing completion. The ICH Guideline for Good Clinical Practice has been adopted by the three lead regions and by many other countries.22 As developing nations begin establishing practices for the testing and registration of new molecular entities, many are using ICH guidelines as standards.

Thus, during the past 50 years, the conduct of clinical drug research has improved because of regulations, guidelines, and policies put in place to protect subjects. Individual pharmaceutical companies have used these guidelines and regulations as the basis for their standard operating procedures (SOPs), technical operations policies, and training programs to direct work processes and staff in their research. Most companies have created quality assurance (QA) units to oversee their researchers’ adherence to agency guidelines and regulations and to their own company policies and practices.

Given the guidelines and regulations in place, how then is the conduct of trials involving humans actually regulated and tracked? And how does the pharmaceutical industry ensure that regulatory standards are implemented and followed?

**Implementing safety standards**

Elements of pharmaceutical company and government agency guidelines and programs that focus on subject safety and the objectivity, integrity, and truthfulness of the data in clinical research are highlighted below.

National regulatory agencies throughout the world publish regulations and guidelines for the conduct of clinical research. These regulations, many of which now include or refer to the ICH Guideline for Good Clinical Practice, specify the way clinical trials are to be conducted, how subject safety is to be ensured, and how data integrity is to be established and maintained. The key underlying premise of these regulations—subject safety—is embodied in the Declaration of Helsinki, which serves as a moral guideline for physicians and researchers.

Pharmaceutical companies instruct employees in the regulations and guidelines and expect them to adhere to the standards in the conduct of their studies. In the United States, no clinical drug research can begin without prior FDA review of the Investigational New Drug application, which includes the human testing protocol and associated preclinical testing results. Regulators in some countries require only notification of intent to initiate first-in-human studies. Before moving on to Phase 2 or Phase 3 studies, pharmaceutical companies and other sponsors must submit the information gathered to date for agency reviews.

**Ethical review.** Wherever human drug research is conducted, national regulations call for an independent ethical review of the study plan. In countries where a guideline on GCP is used, ethics review bodies are made up of medical professionals from the institution, nonmedical personnel, and community members.

Sponsor companies and involved investigators have no voting representation on these review boards, nor may they be present during the voting on the research approval. The investigator conducting the study may, however, present the protocol and answer questions at the IRB review meeting. The company sponsoring the trial is not allowed to participate in IRB meetings as a matter of routine, although a representative might be invited to explain or clarify the protocol to the ethics review body.

**Informed consent** must be obtained from study participants—in writing—before any study-related activities are performed. Regulations clearly describe the required elements of the consent document and the consent process to be followed. A good informed consent process can help ensure that potential subjects understand the nature of the studies they will enter, the type of treatments they will undergo, alternative therapies currently available, and any particular hazards they might experience. They must be informed that they can withdraw from the study at any time without penalty. Subjects are to be asked for their consent to release information from their medical records and told that the medical information may be inspected by sponsor company and regulatory agency representatives. They are to be informed that the results of the trial may be used publicly, but anonymously.

**Drug supplies** must be accounted for throughout the trial and reconciled at the end of the trial. These practices are designed to prevent the misuse or inappropriate redistribution of the investigational drug and to help ensure compliance with the protocol.

**Adverse events.** All adverse events, unexpected drug reactions, and drug side effects experienced and reported by subjects or observed by clinical investigators are to be recorded and promptly reported to sponsor companies. The investigators involved with subject care and the pharmaceutical company sponsor are then to analyze each event for “causality” and “relatedness” to administration of the drug—did this reaction occur because of the drug or because of something else such as the progression of the disease symptoms, other medications being taken, or unrelated causes? Such safety information is then to be forwarded to the
appropriate IRB or ethics committee and regulatory agencies. The sponsor company is to send periodic updates to investigators, alerting them to new serious or unexpected drug reactions.

Company physicians are expected to continuously analyze the adverse drug event data coming in from worldwide trials for trends and patterns that could foretell a drug safety problem. Drug companies frequently set up data and safety monitoring boards (DSMBs), composed of noncompany medical experts and statisticians who impartially evaluate safety as the study progresses and are responsible for alerting the sponsor to unanticipated problems. Regulatory agencies also watch for trends, because they are often in the best position to see safety trends across classes of drugs from many different companies.

**Quality assurance.** Sponsor companies use quality assurance units independent of the clinical research group to audit medical operations. Their role is to ensure that regulatory standards and company policies and procedures for clinical research are being followed in all countries where research is being conducted.

**Regulatory oversight.** Government agencies oversee sponsor organizations, clinical trial processes, and clinical trial sites to verify that sponsors are conducting trials appropriately. When deficiencies are noted, agency inspectors can restrict and penalize the offending academic institution, contract research organization (CRO), institutional review board, investigator, and/or the sponsor company. Investigator sites can be prohibited from conducting clinical research. Company studies can be rejected by regulatory agencies.

**Continuous safety monitoring**

**Site staff examinations.** Medical staff members at the clinical trial site and at the sponsor company are expected to be continuously alert to adverse drug reactions or unexpected and serious medical problems that might be attributed to the new medication being tested. The investigator and the site staff examine subjects and take vital sign measurements on the schedule designated by the protocol, the guide for study conduct. Each drug, as shown in its preclinical studies, has unique characteristics, and the potential for adverse events or side effects that investigators need to watch for during the clinical trial.

For that reason, safeguard activities are built into the protocol, such as the time intervals between subject visits, how often subjects are to be questioned and examined, the specific medical tests to be run at various time points, and the special diagnostic tests or interviews to be conducted. Staff members at the clinical site must record the medical information from these tests and from interviews and medical histories. Site staff must also transfer information from the medical source documents to the case report forms (CRFs) specific to the study. The CRFs contain key information requested in the protocol. Clinical research associates and physicians are required to review the information regularly and to immediately report anything alarming to the IRB and regulatory agencies for further evaluation.

**Sponsor pharmacovigilance.** Dedicated departments in pharmaceutical companies—often called pharmacovigilance groups—receive, review, analyze, follow up on, and appropriately distribute safety-related information from new drug trials. These groups sometimes staff hot lines and Q&A services to provide up-to-date answers to drug-related questions. Safety information is to be reported to regulatory agencies at specified intervals and at milestone time points throughout all phases of drug development. A company’s pharmacovigilance operations are subject to detailed oversight by the company’s independent quality assurance units and are often inspected by FDA.

**Sponsor monitoring** is another important oversight process to ensure quality, compliance, and subject safety. Monitors may be employees of the sponsor’s medical staff or a contract research organization, or may be independent contractors. In each case, they represent the sponsor, and visit investigator sites regularly, perhaps every four to eight weeks. They examine subject records in detail and verify that the correct information was transferred to the clinical trial case report forms—a process called *source data verification*. During their site visits, monitors also examine administrative and regulatory documents, including drug supply and dosing records, adverse events documentation and reporting, the informed consent process, and communications between the sponsor company and investigator and between the investigator and IRB. In short, the activities of clinical trial monitors are designed to ensure that all elements of the protocol are being followed. In addition, monitors examine the appropriateness of the qualifications, training, and training records of all site staff involved with the trial, and they communicate changes in site personnel to the sponsor company’s oversight team.

Following the completion of a site monitoring visit, the monitor meets with the site staff to review findings and discuss (agree upon) corrections in data or improvements in processes, if needed. Monitors are expected to write a formal monitoring report promptly after each visit. Reports are sent to the sponsor company’s medical department, which reviews the reports. When necessary, that department’s clinical research associates and physicians recommend remedial action.

Regular monitoring ensures continued contact with an investigator site to keep the sponsor company aware of the site’s safety and compliance status. Periodically, information from many monitoring visits and reports is gathered and analyzed for common problems. When problems are detected, special site- or trial-specific counseling and training is initiated.

**Quality assurance**

As stated in the ICH guideline for GCP, and as recommended by the FDA, each pharmaceutical sponsor company is to have a quality assurance unit that is independent of the operational area—that is, outside the company’s clinical research group. The function of the QA unit is to conduct independent assessments and audits to ensure that appropriate clinical research processes are in place and that clinical operations are being conducted according to relevant regulations and guidelines, and in conformance with the sponsor’s corporate policies, procedures, and trial protocol. QA is to report any variations or deviations it finds to the operational area staff and management and, periodically, to the company’s senior management.

All major pharmaceutical companies have independent QA departments. Many have staff members based throughout the world. A portion of the mission statement of one such group, the quality assurance
some groups report directly to the company CEO, and some to a vice president of quality.23 Many companies also have a compliance or ethics hot line that employees can call (anonymously, if desired) 24 hours any day to relate an observation or lodge a complaint or concern. These “call-ins” are then investigated to closure.

Although organizationally separate from the clinical research component, QA personnel work closely with clinical operations to understand its internal processes and activities and to learn the locations of trial sites and site-related activities. It is important for the QA department to know “where the action is,” and to be there frequently enough to ensure that things are done properly. This means compiling a list of clinical operations group activities and conducting a formal or informal risk assessment to determine which processes and areas are best under control. Examples of risk factors are investigators new to clinical research who require further training and sites with high staff turnover, which can lead to uncertainties and mistakes in clinical trial practice. QA personnel can then conduct planned audits of sites and medical processes and write reports for QA management review. The management and staff of the audited group receive final reports of the audit findings, as do designated senior managers throughout the company.

In some cases, “special alert” notations may be marked on audits to trigger specific and prompt action by senior corporate managers. In fact, all audit findings require some response, such as who will address the issue, what the action plans are, and when they will be completed. The QA department tracks the action plans to completion with the goal of continual improvement in quality, compliance, and safety reporting.

When the auditors come

Both the company’s own QA auditors and the regulatory agency inspectors examine many facets of the clinical trial during their visits to an investigator site. The oversight activities of the company’s monitoring and QA groups overlap considerably—as they should. Monitors, auditors, and inspectors all assess quality and compliance through examination of medical records and test results, and by interviewing the site’s medical staff (see Monitor Questions box).

QA auditors and clinical research department monitors are especially alert to the safety aspects of the trial. Specifically:

• Were subjects appropriately informed of the risks in the clinical trial?
• Were subjects told about available alternative therapies?
• Were subjects seen on schedule for check-ups, treatments, and evaluations?
• Are qualified staff seeing the subjects and conducting appropriate tests?
• Were all diagnostic tests completed and on schedule?
• Is the physician in charge—rather than less-qualified members of the investigator’s staff—administering and analyzing diagnostic tests and evaluations?
• Are subjects completing their daily diaries, and are the diaries given to the clinical trial physician for examination?
• Is medication being dispensed in the appropriate doses and at the right intervals?
• Did the practicing physician exclude other medications that might interfere with (or be hazardous in combination with) the experimental drug, and did the subject indeed avoid them?
• Did any drug reactions or adverse events occur during the trial? Were these appropriately noted and reported to the pharmaceutical sponsor company?
• Is the clinical research physician at the sponsor company appropriately reviewing safety information across the entire clinical trial to detect negative trends or safety concerns?
• Did the sponsor company summarize
and report adverse events, if warranted, to the regulatory agencies?
• Did the clinical investigator receive periodic or spontaneous adverse event safety updates from the sponsor company?
• Did the investigator share the safety updates with the clinical staff and forward them to the institutional review board?

When things go awry
Every complex, multicomponent operation faces the possibility that, from time to time, things may not go as planned. This may result from failures in the sponsor’s planning, monitoring, or follow-up; from providing poorly written instructions to the trial site; or from a failure of investigator site physicians or staff to conduct the study according to plan. Study subjects themselves are critical parts of the clinical trial process; they must store and take medication properly, complete their paperwork, answer questions truthfully and correctly, and return to the site for visits on schedule.

At times, but rarely, some party in the clinical trial process commits outright fraud. Sometimes the sponsor’s monitoring staff or the QA auditing group detects such serious scientific misconduct, but most often a member of a site’s staff sees or senses misconduct and reports it to a sponsor or regulatory authorities. “Whistle-blowers” may come forward to the sponsor’s monitors with the first mention of a problem—reporting, for example, that people are not following the protocol or are not complying with regulations designed to ensure appropriate medical care and subject protection. When this occurs, the sponsor company’s QA department takes prompt action to investigate the allegation and identify (in great detail) the “who, what, when, and where” of the incident. The first goals of the investigation are to ensure appropriate subject safety and medical care, and then to determine whether it is possible or desirable to continue the trial at a given site—that is, can good subject care be ensured? Figure 2 shows an example of the sequence of events in the investigation of alleged scientific misconduct.

Once they have gathered the facts, the sponsor’s QA personnel and the clinical research staff meet to address the issues and to determine an appropriate resolution. When subjects are receiving benefit from an experimental therapy, one option is to continue the trial, but under the direction of a new site or staff. Other options are to cease work at a particular institution or to add remedial training and closer monitoring to improve operations in areas of marginal compliance.

Safety first
Ensuring subject safety, as well as demonstrating the effectiveness of a new medication, is of the utmost importance throughout the entire drug development process. Safety concerns factor into the initial strategic thinking of the discovery research chemists and pharmacologists. Then, toxicologists conduct numerous short- and long-term toxicology and safety studies in animals before dosing the first human being. Such studies continue throughout the clinical trial to expand the knowledge base for a given drug. The gradual dose escalation of a drug candidate in healthy human volunteer subjects is performed under tightly controlled conditions and under the direction and scrutiny of highly trained clinical pharmacology physicians. A drug candidate’s progress toward broader testing in a population of individuals with the disease or condition to be treated also moves cautiously and gradually.

An overarching focus on safety and the documentation of safety-related information is built into clinical research protocols, case report forms, databases, and
alerting systems within pharmaceutical sponsor companies. Safety and pharma-
covigilance physicians engage in ongoing analysis of safety data, analyzing it across
clinical trial sites and subject populations to detect any trends or early warning
signs of problems. Throughout the develop-
ment process, information flows contin-
ually between sponsor companies and the
regulatory agencies that will eventually
decide whether to grant marketing
approval to the sponsor company.

The sponsor company’s QA unit over-
sees the quality and compliance of the
overall drug development process. These
units—which are independent of clinical
research operations and staffed by scient-
ists with special training in compliance,
inspection, and auditing—are committed to
upholding high standards of regulatory
compliance and basic corporate ethics.
Regulatory agencies throughout the
world also inspect sites and sponsors to
assure themselves that the regulations
were followed and that sound data was
submitted for decision-making.

Those who contribute to the develop-
ment of an effective new drug—one that
improves the health and well-being of
their fellow human beings—take pride in
helping to move an idea to reality. And
they take equal pride in the fact that the
new drug was developed without harm to
the multitude of clinical trial subjects who
voluntarily took part in the quest for
improved therapy.

References
1. Sandy Hodson, “Ex-MCG Doctors Face
Suit Over Drug Study,” The Augusta
Chronicle (30 January 2001); online at
http://augustachronicle.com/stories/
013001/met_192-5942.000.shtml.
2. Kurt Eichenwald and Gina Kolata, “A Doc-
tor’s Drug Studies Turn Into Fraud,” New
3. Letter from the NIH Office for Protection
from Research Risks to UIC Chancellor
David Broski and Provost Elizabeth Hoff-
man (27 August 1999); online at www.uic.
edu/depts/oprr/oprr8-99.html.
4. Eric A. Gislason and Brenda Russell, “UIC
Priorities and Processes Immediate and
Short Term Plans,” University of Illinois at
Chicago Human Subjects Protection Bul-
letin (8 September 1999).
5. Letter from OPRR to VA Greater Los
Angeles Healthcare System Office of Pro-
tection from Research Risks (22 March
1999).
6. Department of Health and Human Ser-
sices, Institutional Review Boards: A Time
for Reform, OEI-01-97-00193 (Office of
Inspector General, Washington DC, June
7. David Malakoff, “Flawed Cancer Study
Leads to Shake-Up at University of Okla-
ahoma,” Science, 289, 706–707 (4 August
2000).
8. Sheryl Gay Stolberg, “F.D.A. Officials
Fault Penn Team in Gene Therapy Death,”
9. Allen Spera, “Blowing the Whistle on
Investigative Sites,” CenterWatch, (7) 8, 1,
5–9 (August 2000).
10. Office of Inspector General, Protecting
Human Research Subjects: Status of Rec-
ommendations, OEI-01-97-00197 (Depart-
ment of Health and Human Services,
Washington, DC, April 2000; online at
11. Office of Inspector General, Recruiting
Human Subjects: Pressures in Industry-
Sponsored Clinical Research, OEI-01-97-
00195 (Department of Health and Human
Services, Washington, DC, June 2000;
online at www.hhs.gov/oiig/oei/reports/
a459.pdf).
12. Adil E. Shamoo, “Future Challenges To
Human Subject Protection,” The Scientist,
14 (13) 35 (26 June 2000); online at
13. Association of American Universities,
Task Force on Research Accountability,
“Report on University Protections of
Human Beings Who Are the Subjects of
Research” (Washington, DC, 28 June
2000; online at www.aau.edu/ HumSubRpt06.28.00.pdf).
‘Intermediate’ Enforcement Authority For
Clinical Trials,” The Pink Sheet, 62 (19)
16–17 (8 May 2000).
15. Jill Wechsler, “Clinical Trial Safety and
Oversight Top Policy Agenda,” Applied
Clinical Trials, January 2001, 18–21; online at
www.actmagazine.com/articles/act/
act0101_jill.pdf.
16. Donna Shalala, “Protecting Research Sub-
jects—What Must Be Done,” The New
England Journal of Medicine, 343 (11)
808–810 (14 September 2000).
17. Jane E. Henney, remarks presented at the
Association of American Medical Colleges
Council of Teaching Hospitals Spring
Meeting, 11 May 2000; online at www.
18. Jane Ganter, “Responding to Industry Crit-
cis: If the industry doesn’t address con-
cerns raised by the consumer press, who
will?” Applied Clinical Trials, November
1999, 10.
19. Pharmaceutical Research and Manufactur-
ers Association (PhRMA), www.phrma.
org/publications/publications/brochure/
questions/whycostmuch.phtml.
20. World Medical Association Declaration of
Helsinki: Ethical Principles for Medical
Research Involving Human Subjects.
Adopted by the 18th WMA General
Assembly, Helsinki, Finland, June 1964;
and amended by the 29th WMA, 1975;
35th WMA, 1983; 41st WMA, 1989; 48th
WMA, Somerset West, Republic of South
Africa, October 1996; and 52nd WMA,
Edinburgh, Scotland, October 2000 (The
World Medical Association, Inc., PO Box
63, 01212 Ferney-Voltaire Cedex, France,
+33 4 50 40 75 75, fax +33 4 50 40 59 37;
e-mail: info@wma.net, www.wma.net/e/
policy/17-c_e.html).
21. Code of Federal Regulations, Title 21,
Parts 50, 54, 56, 312, 314 (U.S. Govern-
ment Printing Office, Washington, DC;
online at www.access.gpo.gov/nara/cfr/).
22. Guideline for Good Clinical Practice,
International Conference on Harmonisation,
Federal Register 62 (901) 25691–25709 (9
May 1997; also available from EMEA, 7
Westferry Circus, Canary Wharf, London
E14 4HB, UK; online at www.emea.eu.int/
23. Samuel T. Barnett and Roger W. Croswell,
“Structuring the Quality Assurance Func-
tion,” Drug Information Journal, 32,

Acknowledgments
I would like to thank members of the Biore-
search Monitoring Committee of the Pharma-
care Research and Manufacturers Associa-
tion (PhRMA) for their opinions and additions,
and also Ms. Stephanie Martin for excellent
administrative assistance throughout the writ-
ing and revision process.

Michael J. Schmidt, PhD, now retired, was
director of quality assurance at Eli
Lilly & Company when this article was
written. He can be reached at (317) 877-
1373, e-mail: drbones5000@aol.com.