Guidelines for the

Conduct of Research

in the

Intramural Research

Program at NIH

National Institutes of Health
Office of the Director

The Guidelines for the Conduct of Research set forth the general principles governing the conduct of good science as practiced in the Intramural Research Programs at the National Institutes of Health (NIH). They address needs arising from the rapid growth of scientific knowledge, the increasing complexity and pace of research, and the influx of scientific trainees with diverse backgrounds. Accordingly, the Guidelines should assist both new and experienced investigators as they strive to safeguard the integrity of the research process.

The Guidelines, originally developed by the Scientific Directors of the Intramural Research Programs at the NIH, have been revised for this edition by the intramural scientists on the NIH Committee on Scientific Conduct and Ethics, and approved by the Scientific Directors. General principles are set forth concerning the responsibilities of research staff in the collection and recording of data, publication practices, authorship determination, mentoring, peer review, confidentiality of information, collaborations, human subjects research, financial conflicts of interest, and animal care and use.

It is important that every investigator involved in research at NIH read, understand, and incorporate the Guidelines into everyday practice. The progress and excellence of NIH research is dependent on our vigilance in maintaining the highest quality of conduct in every aspect of science.

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

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Introduction

Scientists in the Intramural Research Programs at the National Institutes of Health generally are responsible for conducting original research consonant with the goals of their individual Institutes and Centers. These Guidelines were developed to promote high ethical standards in the conduct of research by intramural scientists at the NIH. It is the responsibility of each Principal Investigator who oversees a research group, and successive levels of supervisory individuals (especially Institute and Center Scientific Directors), to ensure that every NIH scientist is cognizant of these Guidelines and to resolve issues that may arise in their implementation.

Intramural scientists at NIH, as is true for all scientists, should be committed to the responsible use of scientific tools and methods to seek new knowledge. While the general principles of scientific methodologies -formulation and testing of hypotheses, controlled observations or experiments, analysis and interpretation of data, and oral and written presentation of all of these components to scientific colleagues for discussion and further conclusions - are universal, their detailed application may differ in different scientific disciplines and in varying circumstances. All research staff in the Intramural Research Programs should maintain exemplary standards of intellectual honesty in formulating, conducting, presenting, and reviewing research, as befits the leadership role of the NIH.

These Guidelines complement existing NIH regulations for the conduct of research such as those governing human subjects research, animal use, radiation, chemical and other safety issues, and the Standards of Conduct that apply to all federal employees.

The formulation of these Guidelines is not meant to codify a set of rules, but rather to elucidate, increase awareness and stimulate discussion of patterns of scientific practice that have developed over many years and are followed by the vast majority of scientists, and to provide benchmarks when problems arise. Although no set of guidelines, or even explicit rules, is likely to prevent willful scientific misconduct, it is hoped that formulation of these Guidelines will contribute to the adoption of exemplary standards of intellectual honesty in the conduct of research by all scientists.

The public and our scientific colleagues will ultimately judge the NIH by its adherence to high intellectual and ethical standards, as well as by its development and application of important new knowledge through scientific creativity. ▲

Responsibilities of Research Supervisors and Trainees

Research training is a complex process, the central aspect of which is an extended period of research carried out under the supervision of an experienced scientist. This supervised research experience is not merely performance of tasks assigned by the supervisor, but rather is a process wherein the trainee takes on an increasingly independent role in the selection, conceptualization and execution of research projects. The trainee should be provided with training in the necessary skills and knowledge necessary for a successful career as a research investigator. It should be recognized that the trainee has unique, time-sensitive needs relevant to career advancement. Guidance and advocacy from the supervisor in this regard are essential components of training.

In general, a trainee will have a single primary supervisor, but may also have other individuals who function as mentors for specific aspects of training and career development. It is the responsibility of the primary supervisor to serve as a role model and provide a rich research environment in which the trainee has the opportunity to acquire both the conceptual and technical skills of the field. In this setting, the trainee should be provided with clear expectations and undertake a significant piece of research, usually chosen as the result of discussions between the mentor and the trainee, which has the potential to yield new knowledge of importance in that field. In order to provide a meaningful, high quality training experience, the mentor should monitor and guide the trainee's progress closely, and interact personally on a regular basis to give timely feedback regarding research findings and progress. Supervisors and mentors should limit the number of trainees in their laboratory or branch to the number for whom they can provide an appropriate and productive training experience. Mentoring should be adapted to the needs and career stage of each individual trainee.

Specific aspects of the mentor-trainee relationship deserve emphasis. Training should impart to the young investigator appropriate standards of scientific conduct both by instruction and by example. Mentors should be particularly diligent to involve trainees in research and related activities that contribute to their careers, including participation in intramural or extramural collaborations, encouragement of presentations at scientific meetings, and networking. Mentors should provide trainees with timely and realistic appraisals of their performance and with advice regarding career opportunities and advancement.

Trainees have responsibilities to their supervisors and to their institutions as well. These responsibilities include adherence to these Guidelines and other applicable rules, and programmatic constraints related to the needs of the research team and Institute/Center. The same standards of professionalism and collegiality apply to trainees as to their supervisors and mentors. ▲

Data Management and Archiving

Research data, including detailed experimental protocols, all primary data, and procedures of analysis and presentation are the essential components of scientific processes and progress. Scientific integrity is inseparable from meticulous attention to the acquisition and maintenance of these research data.

The results of research should be carefully recorded in a form that will allow continuous access for analysis and review. When possible, it is best to store data in both electronic and hard-copy form. Attention should be given to annotating and indexing notebooks and documenting computerized information to facilitate detailed analysis and review of data. All data, even those from observations and experiments not directly leading to publication, should be treated comparably. All research data should be available to supervisors and scientific collaborators for timely review, consistent with requirements of confidentiality. Investigators should be aware that research data are legal documents for purposes such as establishing patent rights or defending the veracity of published results, and are subject to subpoena by congressional committees and the courts.

Research data, including the primary experimental results and computer and statistical analyses, should be retained for a sufficient period to allow analysis and repetition by others of published material resulting from those data. Seven years is specified by the Federal Government (http://www.ori.dhhs.gov/documents/FR_Doc_05-9643.shtml) as the minimum period of retention but this may be longer under some circumstances, such as clinical research.

Notebooks, other research data, and supporting materials, such as unique reagents, belong to the National Institutes of Health, and should be maintained and made available, in general, by the Laboratory in which they were developed. Departing scientists may take copies of notebooks or other data for further work. Under special circumstances, such as when required for continuation of research, departing investigators may take primary data or unique reagents with them if adequate arrangements for their safekeeping and availability to others are documented by the appropriate Institute or Center official. Transfer of reagents should be documented through a Material Transfer Agreement.

Data management, including the decision to publish, is the responsibility of the principal investigator. After publication, the research data and any unique materials that form the basis of that communication should be made available promptly and completely to all qualified scientists seeking further information. Exceptions may be necessary to maintain confidentiality of clinical data or if unique materials were obtained under agreements that preclude their dissemination. Consult the PHS policy relating to the distribution of unique research resources for further guidance (http://grants2.nih.gov/grants/guide/notice-files/not96-184.html). ▲

Publication

Publication of results is an integral and essential component of research. Other than presentation at scientific meetings, publication in a scientific journal should normally be the mechanism for the first public disclosure of new findings. Exceptions may be appropriate when serious public health or safety issues are involved. Although generally considered the end point of a particular research project, publication is also the beginning of a process in which the scientific community at large can assess, correct and further develop any particular set of results.

Timely publication of new and significant results is important for the progress of science. Fragmentary publication of the results of a scientific investigation or multiple publications of the same or similar data are inappropriate. Each publication should make a distinct and substantial contribution to its field. As a corollary to this principle, tenure appointments and promotions should be based on the importance of the scientific accomplishments and not on the number of publications in which those accomplishments were reported.

Each paper should contain sufficient information for the informed reader to assess its validity, including all the information that would be necessary for scientific peers to repeat the experiments. Essential data that are not included in the published paper due to space limitations (e.g. nucleic acid and protein sequences, microarray data and crystallographic information) should be deposited in the appropriate public databases or made available online. It is not necessary to provide materials (such as proteins) that others can prepare by published procedures, materials (such as polyclonal antisera) that may be in limited supply, or clinical specimens (whose distribution is controlled by human subjects protection requirements, as described in a later section). However, it is an obligation of NIH intramural scientists to make reasonable amounts of expandable materials (e.g. monoclonal antibodies, bacterial strains, mutant cell lines) and analytical amounts of reagents (e.g. polyclonal antibodies, purified proteins, uniquely-synthesized compounds) that are essential for repetition of the published experiments available to qualified scientists, using appropriate Material Transfer Agreements or collaborative agreements consistent with NIH policy. This can be achieved by making arrangements to send such materials to a central repository. Consult the PHS policy relating to the distribution of unique research resources for further guidance (http://grants2.nih.gov/grants/guide/notice-files/not96-184.html).

The current NIH Public Access Policy (http://publicaccess.nih.gov/publicaccess_manual.htm) requests and strongly encourages all NIH-funded investigators to make their peer-reviewed final manuscripts available to other researchers and the public at the NIH National Library of Medicine's (NLM) PubMed Central (PMC) (http://www.pubmedcentral.nih.gov) immediately after publication of the final version. Authors are given the option to release their manuscripts at a later time, up to 12 months after the official date of final publication. NIH expects that only in limited cases will authors deem it necessary to select the longest delay period. ▲

Authorship

Authorship refers to the listing of names of participants in all communications, both oral and written, of experimental results and their interpretation to scientific colleagues. Authorship is the fulfillment of the responsibility to communicate research results to the scientific community for external evaluation. Authorship is also the primary mechanism for determining the allocation of credit for scientific advances and thus the primary basis for assessing a scientist's contributions to developing new knowledge. As such, it potentially conveys great benefit, as well as responsibility.

For each individual the privilege of authorship should be based on a significant contribution to the conceptualization, design, execution, and/or interpretation of the research study, as well as on drafting or substantively reviewing or revising the research article, and a willingness to assume responsibility for the study. Individuals who do not meet these criteria but who have assisted the research by their encouragement and advice or by providing space, financial support, reagents, occasional analyses or patient material should be acknowledged in the text but not be authors. These authorship guidelines are comparable to those now described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which were developed by the International Committee of Medical Journal Editors (http://www.icmje.org/).

Because of the variation in detailed practices among disciplines, no universal set of standards for authorship can easily be formulated. It is expected, however, that each research group and Laboratory or Branch will freely discuss and resolve questions of authorship, including the order of authors, before and during the course of a study. Further, each author should review and support the manuscript that is to be submitted (originally or in revision) for publication. Each author should be willing to support the general conclusions of the study. The NIH recommends that the transmittal letter accompanying a manuscript submission identify the exact contribution of each author.

The corresponding author should be considered the primary author (but is not necessarily the first author), with the additional responsibilities of coordinating the completion and submission of the work, satisfying pertinent rules of submission, and coordinating responses of the group to inquiries or challenges. The corresponding author should assure that the contributions of all collaborators are appropriately recognized and that each author has reviewed and authorized the submission of the manuscript in its original and revised forms. Corresponding authors must be especially vigilant that the above criteria are met before sending articles to journals that publish submissions on line upon acceptance of the manuscript.

All manuscripts and abstracts coming from the Intramural Research Program must be cleared in accordance with the instructions included at http://www1.od.nih.gov/oir/sourcebook/oversight/pub-clear.htm. ▲

Peer Review and Privileged Information

Peer review is expert critique of either a scientific treatise, such as an article prepared or submitted for publication, a grant proposal, or a clinical research protocol, or of an investigator's research program, as in a site visit. Peer review is an essential component of the conduct of science. Decisions on the funding of research proposals and on the publication of experimental results must be based on thorough, fair and objective evaluations by recognized experts. Therefore, although it is often difficult and time-consuming, scientists have an obligation to participate in the peer review process. In doing so, they make an important contribution to science.

Peer review requires that the reviewer be expert in the subject under review. The reviewer should avoid any real or perceived conflict of interest that might arise because of a direct competitive, collaborative or other close relationship with one or more of the authors of the material under review. Normally, such a conflict of interest would require a decision not to participate in the review process and to return any material unread. Some review activities may require review and approval by a supervisor and/or deputy ethics counsellor in an IC (see http://www1.od.nih.gov/oir/sourcebook/ethic-conduct/officialdutypolicy.htm).

The review must be objective. It should be based solely on scientific evaluation of the material under review within the context of published information and should not be influenced by scientific information not publicly available.

All material under review is privileged information. It should not be used to the benefit of the reviewer unless it previously has been made public. It should not be shared with anyone unless necessary to the review process, in which case the names of those with whom the information was shared should be made known to those managing the review process. Material under review should not be copied and retained or used in any manner by the reviewer unless specifically permitted by the journal or reviewing organization and the author. ▲

Collaborations

Collaborative research brings together investigators with distinct strengths to work together on a defined problem or address a specific research goal. Research collaborations, within NIH as well as with extramural institutions, are strongly encouraged and supported; the complex scientific questions that face us today often require interdisciplinary or multidisciplinary approaches.

Successful collaborations are characterized by a strong sense of direction, a willingness to commit time and effort, an efficient communication strategy for discussion among the group members, a system in place for reevaluation as the project progresses, and a clear definition of roles and responsibilities. It is advisable that the ground rules for collaborations, including eventual authorship issues, be discussed openly among all participants from the beginning. The NIH Ombudsman Office has developed a useful set of criteria to consider in establishing collaborations (http://www4.od.nih.gov/ccr/collab.html).

Whenever collaborations involve the exchange of biological materials they are routinely formalized by written agreements. Material Transfer Agreements (MTAs) are used for the simple transfer of proprietary research material without collaboration, for example if you request a reagent from, or give one to, a colleague outside the NIH. Cooperative Research and Development Agreements (CRADAs) are agreements between one or more NIH laboratories and at least one non-federal group (private sector, university, not-for-profit, non-federal government). CRADAs provide a protected environment for long-term collaborations; they confer intellectual property rights to NIH inventions. CRADAs are handled by the Technology Transfer Office of your Institute (http://ott.od.nih.gov/).

Consulting can be viewed as a one-way collaboration, in which an NIH scientist is asked to contribute to an outside project by providing expert advice. Information about the NIH guidelines governing consulting activities and forms for obtaining permission can be found at http://ethics.od.nih.gov/ ▲

Financial Conflicts of Interest

Real or perceived conflicts of interest due to financial relationships with outside organizations may not be recognized by others unless specific information is provided. Therefore, the scientist should disclose all relevant financial interests, including those of the scientist's immediate family, to the Institute or Center during the planning, conducting and reporting of research studies; to funding agencies before participating in peer review of applications for research support; to meeting organizers before presentation of results; to journal editors when submitting or refereeing any material for publication; and in all written communications and oral presentations. Financial interests include, but are not limited to, ownership of stock or equity, patents, consulting arrangements, collaboration agreements, honoraria, service on advisory boards, or management appointments. Failure to disclose conflicts of interest can threaten the integrity of research and undermine the public's trust in the NIH's intramural research activities. When there is a potential conflict of interest, full disclosure and complete transparency are always the best policy. The NIH's Ethics Program (http://ethics.od.nih.gov/) has specific rules concerning conflicts of interest, outside activities (such as consulting and speaking), gifts, honorary awards, and investments. Intramural researchers should become familiar with these rules and refer any questions to the Deputy Ethics Counselor of their Institute or Center.

A specific ***Guide to Preventing Conflicts of Interest in Human Subjects Research at NIH*** covers participation in human subjects research in the Intramural Research Program (http://intranet.cc.nih.gov/od/conflict_interest/conflict_memo.shtml). ▲

Human Subjects Research

For the purposes of these Guidelines, clinical research is defined as interactions with human subjects, or with material or information obtained from human subjects, in order to produce generalizable knowledge. This is distinguished from interactions designed solely to benefit a particular patient. The NIH Intramural Research Program has a formal human research protection program supervised by the Office of Human Subjects Research (OHSR). All intramural research must be consistent with the requirements of the human research protection program and all intramural investigators are responsible for knowledge of, and compliance with, them. OHSR can help investigators understand and comply with the ethical guidelines and regulatory requirements for clinical research.

All scientists working with human samples/subjects must take the course "Protecting Human Subjects" (http://ohsr.od.nih.gov/researcherCBT/intro.html?myIPNum=128231088007). In addition, OHSR has published a booklet "Guidelines for the Conduct of Research Involving Human Subjects at the NIH" (http://ohsr.od.nih.gov/guidelines/GrayBooklet82404.pdf) to assist those doing clinical research.

Investigators involved in clinical research have special responsibilities regarding the preparation of research protocols, registration of clinical trials, protection of human subjects, supervision of trainees, collection and storage of research data, and conduct of epidemiologic research. These responsibilities are briefly discussed below.

Protocols: Investigators must prepare a written clinical research protocol describing the scientific background, objectives, subject eligibility criteria, design, methods of data collection and analysis, risks and benefits of the proposed research, and qualifications of the investigators. The protocol must undergo IC-specific scientific review and then be reviewed and approved by the IC Institutional Review Board (IRB) (unless the research is specifically exempt by the OHSR because it does not qualify as human subjects research, e.g., when samples are fully anonymized). All clinical studies require that informed consent be obtained from prospective subjects prior to commencing the research. Studies using investigational drugs or devices must also be reviewed and approved by the Food and Drug Administration (FDA).

Collection and Storage of Data: Investigators must ensure the integrity and confidentiality of data collected in the course of clinical research, and protect the privacy, as well as safety, of human subjects. Attention should be paid to appropriate storage and retention of research records, data, and samples, in accordance with NIH and FDA guidelines. Investigators are responsible for the oversight of all research personnel involved in the clinical study, ensuring that they adhere to the research protocol and Good Clinical Practice[1].

Intramural investigators who receive human samples or data from extramural investigators are responsible for ensuring that they were collected in accordance with ethical guidelines and regulatory requirements. This is usually satisfied by a clinical research protocol and consent document approved by an IRB at the extramural institution, but sometimes may require a parallel clinical research protocol at the NIH. Similar protections are required prior to sending personally identifiable human samples or data to extramural collaborators. The IC IRB and OHSR should be consulted prior to

any transfer to determine the appropriate review and approval mechanisms. Specific regulations govern the use of archival materials (http://ohsr.od.nih.gov/info/DDIR_memo.html).

Registration of Clinical Trials: Clinical trials (i.e., studies evaluating the safety or efficacy of a diagnostic test or treatment intervention) should be registered with a public trials registry (e.g., www.clinicaltrials.gov).

Epidemiologic Research: Epidemiologic research, the study of the distribution and determinants of disease in groups of individuals, presents special challenges for investigators. Although epidemiologists are not usually responsible for clinical care, they must nevertheless ensure that epidemiologic investigations do not interfere with the clinical care or privacy of patients. The epidemiologist must ensure that abnormal findings that could affect a subject's health and require medical attention are dealt with appropriately. Data on diseases, habits, and behavior must be presented and published in a way that protects the identity of particular individuals, families, and groups.

Although it is the practice of some journals not to publish research findings that have been partially released to the public, it may be necessary for reasons of immediate public health considerations to report the findings of epidemiologic research to the study participants, institutional leadership, other researchers, and, in some cases, health officials, before the study has been completed. The health and safety of the public has precedence.

Development and review of detailed protocols are as important in epidemiologic research as in clinical research and any other health science. However, the time for protocol development and review may be appropriately shortened in circumstances such as the investigation of an acute epidemic or toxicological danger where the epidemiologic investigation may provide data of crucial importance to the identification and mitigation of a threat to public health. Nevertheless, even in these situations, systematic planning is necessary and the investigator should formalize the study design in a written document and have it peer-reviewed in an expedited manner before the research is begun. ▲

[1] Guidelines for Good Clinical Practice, developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) can be accessed at www.ICH.org.

Animal Care and Use

The use of laboratory animals is often essential in biomedical research and humane and effective use of animals is a necessary and important element of such research activities. Animal research, for the purposes of these Guidelines, is defined as *in vivo* research performed on laboratory animals in order to develop knowledge that contributes to improvement of health and well-being of humans as well as other animals. The NIH Office of Animal Care and Use (OACU) (http://oacu.od.nih.gov/) has developed NIH Policy Manuals for Animal Care and Use in the Intramural Program to assist NIH intramural investigators to understand and comply with the ethical guidelines and regulatory requirements for testing, research or training involving laboratory animal subjects. The use of animals in research is covered by protocols that must be reviewed and approved by an NIH Animal Care and Use Committee (ACUC). Investigators conducting animal research must take the NIH course "Using Animals in Intramural Research".

The animal care and use program of each IC is directed by a senior veterinarian, the Animal Program Director, and falls under the oversight of an ACUC. All components of the intramural NIH Animal Care and Use program are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Prior to commencing animal studies, an animal study protocol must be prepared according to existing guidelines. Investigators should contact the IC ACUC for guidance on the requirements for approval and implementation of animal study protocols. When developing research proposals involving animals, investigators should consider alternatives to the use of animals based upon the following guidance:

- Reduction: Reduction in the numbers of animals used to obtain information of a certain amount and precision;
- Refinement: Decrease in the incidence or severity of pain and distress in those animals that are used;
- Replacement: Use of other materials, such as cell lines or eggs, or substitution of a lower species, which might be less sensitive to pain and distress, for a higher species.

The animal research protocol should be circulated for comment and review by the investigators and collaborators involved in the project, and requires approval by the IC ACUC prior to study initiation. It should be scrupulously adhered to in the conduct of the research, which should be carried out by appropriately qualified investigators and staff who are experienced in conducting procedures on living animals. ▲

Research Misconduct

The scientific community and general public rightly expect adherence to exemplary standards of intellectual honesty in the formulation, conduct, reporting and reviewing of scientific research. Investigators must act with honesty and integrity when editing, analyzing, and presenting data. Deceptive manipulation of data, be it misrecording of data, inappropriate exclusion of outlying data points, or enhancement of images is research misconduct.

Allegations of scientific misconduct are taken seriously by the National Institutes of Health. The process of investigating allegations must be balanced by equal concern for protecting the integrity of research as well as the careers and reputations of researchers. The procedures followed at the NIH are intended to permit allegations of scientific misconduct to be processed promptly, confidentially, and fairly. Prompt action on an allegation helps minimize any harm to the public that could result if misconduct is found that has potential impact on health, and allows those who are incorrectly implicated to have their names cleared without going through a lengthy process. Allegations of misconduct that are shown to be untrue, even if they were made in good faith, can damage careers and have a chilling effect on research. Confidentiality helps protect both the innocent scientists who are incorrectly or unjustly accused and those who raise the allegations. Fairness allows all who become involved in scientific misconduct cases to have the opportunity to participate appropriately in this important oversight process and address the specific issues at hand, while at the same time protecting innocent participants from adverse consequences.

Scientific misconduct or misconduct in research - Research misconduct is defined as *fabrication*, *falsification*, or *plagiarism* in proposing, performing, or reviewing research, or in reporting research results.

Fabrication is making up data or results and recording or reporting them.

Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

Research misconduct does not include honest error or honest difference of opinion.

(from Federal Policy on Research Misconduct <http://www.ori.dhhs.gov/documents/42_cfr_parts_50_and_93_2005.pdf>) ▲

Concluding Statement

These Guidelines are not intended to establish rules or regulations. Rather, their purpose is to provide a framework for the fair, open, and responsible conduct of research without inhibiting scientific freedom or creativity.

Advice on any of the topics can be obtained from the offices cited in the previous sections. You can consult with members of the NIH Committee on Scientific Conduct and Ethics (http://www1.od.nih.gov/oir/sourcebook/comm-adv/sci-conduct.htm), with your Scientific Director or with your IC Training Director. Advice is also available from the NIH Office of the Ombudsman (http://www4.od.nih.gov/ccr/). ▲