Guidelines for Investigators in Clinical Research

INTRODUCTION

These guidelines outline principles that should be followed at Harvard Medical School when conducting research. They are a supplement to the Guidelines for Investigators in Scientific Research, first issued in February 1988. Clinical research may be defined as investigations involving human subjects or the use of patient samples. The scientific practices described here are generally accepted by investigators conducting both multi-center and single-institution clinical studies and help ensure both the quality and integrity of scientific findings in clinical research. The guidelines are not intended to relieve investigators of any ethical obligations that may be imposed by individual Institutional Review Boards overseeing the rights of study subjects in clinical research.

A major component of clinical research consists of either prospective clinical trials or retrospective studies based on medical or administrative records. Of these two types of studies, prospective trials contain fewer chances for investigator bias and for lost or incomplete data than do retrospective studies, and are to be preferred whenever they are feasible. Some phenomena, however, such as rare diseases or diseases requiring exceptionally long follow-up, can only be studied from a case series assembled from medical records. These guidelines address issues that arise in both types of studies.

The implementation of these guidelines rests within each of the affiliated institutions and the department in which the research is conducted. Whenever research is carried out by non-faculty, such as a student or fellow, the supervisor of that individual is responsible for ensuring that these guidelines are followed.

I. EXPERIMENTAL DESIGN

Successful clinical studies acknowledge the complexity of conducting scientific research with human subjects, and are based both on the principles of experimental design and on respect for the rights of study subjects. Experiments in human subjects generally have highly variable outcomes, and efficient designs that lead to unbiased conclusions are critical.

Recommendations

1. Each study, whether it be observations on one or more patients, a randomized trial, or a population based study, should have clearly articulated research objectives that can be achieved from a successful execution of the study design.
2. Whenever some aspects of a study involve clinical or scientific specialties outside the expertise of the investigator, drafts of the protocol or research plan should be circulated to specialists in those areas for review and comment.
3. Every prospective or retrospective clinical study should have a written protocol or research plan that states the goals of the study, provides a background and rationale for the study, specifies the criteria for inclusion or exclusion of cases, outlines the methods and timings of follow-up, gives a precise definition of the types of anticipated outcome measures, and gives the details of the statistical design. The study design should

minimize the possibility for investigator bias in the interpretation of the results. The design specification may range from a description of anticipated measurements in an exploratory study to a precise specification of the number of cases that will be registered in a phase III randomized trial. In the case of prospective trials, the protocol should describe in detail how patients are to be treated or managed. Any substantial changes to the conduct of the study, including modifications of the sample size, eligibility criteria, or treatment regimens, should be reflected in amendments made to the protocol or research plan and approved by co-investigators and the Institutional Review Board.

4. In randomized clinical trials, the sequence of treatment assignments should be prepared by a statistician or other experienced investigator associated with the trial and kept confidential. In no instance should an investigator treating patients on the trial know the sequence of potential treatment assignments.

5. Clinical studies all require approval of local Institutional Review Boards. Every prospective clinical study should contain an Informed Consent form that explains in clear, non-technical terms the possible risks and benefits for subjects participating in the trial.

II. DATA MANAGEMENT AND TRIAL MONITORING

Complete and accurate data are an essential part of the record of any clinical research. Since serious problems can occur when data are missing or are not consistent with source medical records, each study should include a plan for the keeping of accurate and well documented data not subject to loss through computer failure or insecure storage.

Recommendations

1. In prospective trials, data should be abstracted from source medical records as the trial proceeds, using data collection forms designed at the outset of the study. Data collection forms should also be used in retrospective record studies.

2. The criteria for the evaluation of study subjects (including the classification of outcome and any treatment side effects) should be specified in the protocol or research plan.

3. Interim review of the data from an ongoing trial should make use of statistical methods that guard against increased false-positive or false-negative reporting rates caused by inappropriate conclusions from preliminary analyses.

4. For research involving primary data collection, the principal investigator should retain original data for as long as practically possible, but never for less than five years from the first major publication or from the completion of an unpublished study. All data should be kept in the research unit responsible for conducting the study. Copies of computer programs and the results from statistical calculations used in research involving nationally gathered survey data should also be kept by research units for a minimum of five years from publication based on these results. After notification to responsible departmental officials, principal investigators may make copies of original data or computer programs for personal use or when moving to another research unit or institution.

5. If primary data are kept on a computer file, backup files should be maintained, preferably at a second site, to prevent loss from computer failure.

III. SCIENTIFIC REPORTING

Writing a manuscript reporting the results of a clinical study is a complex and demanding task. Unclear or ambiguous reports reduce the value of a study and may lead to a discrediting of the research.

Recommendations

1. The statistical analysis used in reporting the results should coincide with the planned analysis used to design the study. Reasons should be given in the manuscript for any different analyses that are used.
2. All cases registered in a clinical trial or records reviewed in a retrospective study must be accounted for in any manuscript reporting the results. Any case not used in the analysis of outcome data should be identified (by case number) and the reason for exclusion noted.

IV. AUTHORSHIP

Clinical studies often involve investigators from several subspecialties, and it may not always be possible for a single investigator to confirm each piece of data used in the report of a trial. While each participating investigator must be actively involved in verifying the sections of a manuscript that discuss his/her specialty area, there must nevertheless be a primary author who is responsible for the validity of the entire manuscript.

Recommendations

1. Criteria for authorship of a manuscript should be determined and announced by each department or research unit. The committee considers the only reasonable criterion to be that the co-author has made a significant intellectual or practical contribution. The concept of "honorary authorship" is deplorable.
2. The first author should assure the head of the research unit or department chairperson that he/she has reviewed all primary data on which the report is based and provide a brief description of the role of each co-author. (In multi-institutional collaborations, the senior investigator in each institution should prepare such statements.)
3. Appended to the final draft of the manuscript should be a signed statement from each co-author indicating that he/she has reviewed and approved the manuscript to the extent possible, given individual expertise.

Adopted in October, 1991

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