Overview of Respiratory Care Research

Robert L Chatburn RRT FAARC

Few health care workers are directly involved in conducing research, but all must be able to read and understand scientific reports in medical journals. They must be familiar with the basic concepts of research in order to practice as professionals. The most important skill is the ability to read and critically evaluate published reports. Health care administrators rely on the results of studies to help solve problems and make decisions about important subjects, such as cost containment, productivity assessment, and continuous quality improvement. Educators must stay current with new technology and its evidence base. Both administrators and educators must be familiar with basic research concepts in order to be informed consumers of research information. Research attempts to find answers using the scientific method. This report describes the steps in the scientific method, the overall plan for conducting scientific research, and some basic skills required to successfully conduct research. *Key words: research, respiratory care, publications, study protocol, institutional review board, writing, research methodology, scientific method.* [Respir Care 2004;49(10):1149–1156.

Introduction

The chances that you, the reader, will become a famous researcher may be slim. About 120,000 people are practicing respiratory therapy in the United States, and about 34,000 of those are members of the American Association for Respiratory Care, but only about 500 of those were involved with presenting research at the 49th International Respiratory Congress in 2003. But every one of those 120,000 respiratory therapists needs to know how to read and understand scientific reports in medical journals. The same holds true for all health care workers. Even if you never conduct a study, you must be familiar with the basic concepts of research in order to practice as a professional whose understanding grows from continuing education.

The 2 purposes of the special articles in this issue of RESPIRATORY CARE are to help you become an educated consumer of medical research and to outline a course of self-study if you want to perform research. If you do want to perform research, the best thing you can do is find a mentor—someone who has experience conducting scientific studies and publishing the results. A mentor can help you turn the ideas in these articles into practical realities.[1]

Academic medicine has 3 basic missions: to heal, to teach, and to discover. Scientific research is the thread running through these 3 basic activities that gives them coherence and meaning.

To Heal: Research and Patient Care

Health care professionals must acquire the knowledge and skills needed to assess the usefulness of new equipment, the effectiveness of patient care, and the adequacy of available teaching materials. *The most important of these skills is the ability to read and critically evaluate published reports.* Without that skill no meaningful evaluation of current practices can be made and no research can be planned.

Growing numbers of clinicians, educators, and administrators are conducting their own investigations and critically examining research done by others. Health care workers are usually involved with the application of research results in the clinical setting. Within the research continuum, however, there are almost infinite opportunities to get involved in seeking the answers to questions relating to the practice of health care.

Health Care Administration

Health care department managers and hospital administrators alike rely on the results of studies to help solve problems and make decisions about important subjects, such as cost containment, productivity assessment, and continuous quality improvement. Evaluating the quality of departmental programs and services is difficult. The Joint Commission on Accreditation of Health Care Organizations demands that health care providers monitor quality scientifically. The Commission defines quality assurance as "a manner of demonstrating consistent endeavor to deliver optimal patient care with available resources and consistent with achievable goals. The correction of deficiencies is inherent to the process." This correction process is accomplished through the careful and rigid manipulation of variables and the measurement of effects; in other words, using the scientific method. Only in this way can the physician, patient, patient's family, hospital, and government administrator be assured of the quality and cost-effectiveness of health care services.

Evaluating New Equipment and Procedures

To meet the changing needs of health care, medical equipment manufacturers introduce to the market new diagnostic and support instruments. Because of the relatively short product life cycle in the market of technical equipment, new products are introduced frequently. But *new* does not necessarily mean *better*. At times the development of new technology outpaces the need for that technology, and when that happens, product marketers have not done their job in accurately assessing demand. Medical professionals must then take the lead in assuring that they are not trying to invent ways to use new equipment. Rather, new equipment should satisfy a well-established need. Although manufacturers often engage in extensive testing and market research, the final burden of proof as to a product's ultimate function and benefit falls to the end users—our patients and us.

Ethics and Research

In the health care industry today we are confronted with a multitude of laws, regulatory constraints, and standards that govern the conduct of the industry and the individuals who work in it. Conducting health care research demands attention to a special set of regulatory and ethical considerations.

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Research involving human subjects invokes legal, ethical, and sociologic concerns related to the safety and protection of the subject's human rights. Research involving animals requires attention to several important concerns as well. Regardless of the type of study subjects, those engaged in medical research must be reminded that the importance of their work should never overshadow but, rather, complement society's health care goals. Procedures must strictly adhere to legal guidelines so that subjects are not exploited. Innovative and controversial research must be ethically conducted and honestly reported. The American Association for Respiratory Care has a code of ethics (Table 1) that all therapists must follow, whether they are involved in research or not.[2]

The Institutional Review Board

When human beings participate in scientific research, the researchers must take great care to ensure that the participants' rights are protected. Institutional review boards (IRBs) consider proposed studies from various perspectives to ensure that no study violates patient rights. The researcher cannot begin an investigation involving human subjects without formal approval from the IRB. An IRB (also known as "institutional review committee," "human subjects review committee," "human investigation committee," or "research surveillance committee") is any committee, board, or other group formally designated by an institution to review proposals for biomedical research involving human or animal subjects. An IRB usually includes administration, staff, and legal representatives from the institution and the surrounding community, who ensure that proposed research is reviewed not only in terms of scientific standards but in terms of community acceptance, relevant law, professional standards, and institutional regulations. The IRB meets regularly to review and approve, request revisions to, or reject study proposals.

The IRB's main functions are to protect the rights, well-being, and privacy of individuals and to protect the interests of the institution. IRB procedures differ among institutions, so researchers must review the guidelines applicable in their own institutions.

Consideration of risks, potential benefits, and informed consent typically occupies the majority of the IRB's time. Before an IRB can approve a research protocol, the following conditions must be met:

1. The risks to the research subject are so outweighed by the potential benefits to the subject, and the importance of the knowledge to be gained, as to warrant a decision to allow the subject to accept those risks.
2. Legally effective informed consent will be obtained by adequate and appropriate methods.
3. The rights and welfare of all subjects will be adequately protected.

The IRB may ask the investigator to modify the original research plan to comply with Food and Drug Administration and Department of Health and Human Services regulations as well as ethical norms. However, the IRB is not a police force. There is a presumption of trust that the approved research protocol will indeed be consistently followed.

An IRB application typically includes the components listed in Table 2. First, a formal research protocol must be established. This description of the study's intended purpose and procedures is then followed by information about the intended subjects, including the sources of potential subjects, the anticipated number of subjects required, a description of the consent procedures, and a description of potential risks and benefits to both the subjects and society.

An integral part of the study protocol, and a necessary component for IRB review, is the patient or subject consent form. Indeed, most IRB comments about proposals concern the wording of the consent form. Informed consent is the voluntary permission given by a person, allowing that person to be included in a research study after being informed of the study's purpose, treatment methods, risks, and benefits.

Table 1. Code of Ethics and Professional Conduct for Respiratory Therapists[2]

In the conduct of professional activities the Respiratory Therapist shall be bound by the following ethical and professional principles. Respiratory Therapists shall:

- Demonstrate behavior that reflects integrity, supports objectivity, and fosters trust in the profession and its professionals
- Actively maintain and continually improve their professional competence, and represent it accurately
- Perform only those procedures or functions in which they are individually competent and that are within the scope of accepted and responsible practice
- Respect and protect the legal and personal rights of patients they care for, including the right to informed consent and refusal of treatment
- Divulge no confidential information regarding any patient or family unless disclosure is required for responsible performance of duty or required by law
- Provide care without discrimination on any basis, with respect for the rights and dignity of all individuals
- Promote disease prevention and wellness
- Refuse to participate in illegal or unethical acts, and refuse to conceal illegal, unethical, or incompetent acts of others
- Follow sound scientific procedures and ethical principles in research
- Comply with state and federal laws that govern and relate to their practice
- Avoid any form of conduct that creates a conflict of interest, and follow the principles of ethical business behavior
- Promote health care delivery through improvement of the access, efficacy, and cost of patient care
- Refrain from indiscriminate and unnecessary use of resources

Table 2. Typical Components of a Proposal to an Institutional Review Board

1. A complete description of the study's intended purpose and procedures to be followed
2. A complete description of potential risks a research subject may incur from participation in the study
3. A description of potential benefits, either direct or indirect, a research subject may incur from participation in the study
4. A description of how data will be handled such that the research subject's identity remains anonymous
5. A statement that the subject may withdraw from the study at any time without a prejudicial effect on his or her continuing clinical care
6. The name and telephone number of the investigator, should any questions arise regarding the subject's participation in the study
7. A copy of the complete informed consent form
8. A list of available alternative procedures and therapies
9. A statement of the subject's rights, if any, to treatment or compensation in the event of a research-related injury

To Teach: Research and Education

Medical colleges are responsible for graduating practitioners who are knowledgeable and current in the practice of their profession. Educators must stay up to date with new ideas and technology that affect the diagnosis and treatment of disease. Before a particular piece of equipment or treatment modality is accepted for introduction to the student, the instructor must first discern whether the claims about its benefits rest on a solid scientific foundation. Keeping abreast of new product developments requires that instructors read and critically evaluate reports and tests of function and reliability. A critical reading of scientific journals provides the basis for their decisions concerning classroom demonstrations, guides, and the planning process. Educators may wish to conduct their own investigations as well.

In order that health care practitioners keep informed of recent developments in cardiopulmonary medicine, hospital department managers must establish and maintain continuing education programs. These in-service programs explore and provide a forum for new trends, ideas, and developments as research is completed in various subjects. Allied health professionals are taking an increasing role in patient education and clinical practice. As they keep current on data relating to, for example, the relationship of cigarette smoking to heart disease or cancer, they can increase the patient's awareness of the appropriateness of particular treatment modalities.

The results of research on health care practices serve to reeducate practitioners and update department procedure manuals. Thus, guidelines are developed to improve clinical competence. This occurs as state-of-the-art data on equipment, care modalities, diagnosis, and monitoring procedures are made available and their validity is tested.

To Discover: The Scientific Method

Research attempts to find answers using the *scientific method*. Science is simply "organized curiosity." The scientific method is the organizational structure by which we formulate questions and answers during experiments. The key purpose of this organizational structure is to allow experiments to be repeated and thus validated or refuted. In this way we develop confidence in our findings. Contrary to popular belief, science does not attempt to *prove* anything. You can never prove the truth of an assumption, simply because you can never test all the factors that could possibly affect it. Scientific theories are never "true" in an absolute sense: they are simply *useful* to various degrees and their life spans are inversely proportional to the amount of research done on them.

The scientific method is a series of steps that lead from question to answer, and then usually to more questions. Figure 1 illustrates the scientific method in the form of an algorithm.

Formulate a Problem Statement

Research projects usually start out as a vague perception of some problem or question. The first step is to refine this vague notion into a concise statement or question, usually only 1 or 2 sentences in length. Think in terms of (a) what you see happening and (b) why it is important. For example, if you find a coin lying on the ground your problem statement might be "I need to identify this coin so I can decide whether to pick it up."

Generate a Hypothesis

The hypothesis is a short statement that describes your supposition about a specific aspect of the research problem. The *hypothesis* is what you *test* with an *experiment*. Nobody knows where hypotheses come from: forming one is a creative act. All you can do is prepare yourself by thoroughly studying all aspects of the problem so your mind becomes a fertile ground for hypotheses to grow. Continuing with our example, we might hypothesize that "The coin is a penny."

Define Rejection Criteria

The purpose of the experiment is to provide data, which you will use to either reject the hypothesis as false or accept it for the time being as a useful (but tentative) assumption. The fact that we can never absolutely prove the truth of a hypothesis leads us to focus on trying to prove it false. We prove a hypothesis is false by comparing the experimental data to a set of criteria we have established before the experiment began. If the experimental data do not meet the criteria, we reject the hypothesis (hence the term "rejection criteria").

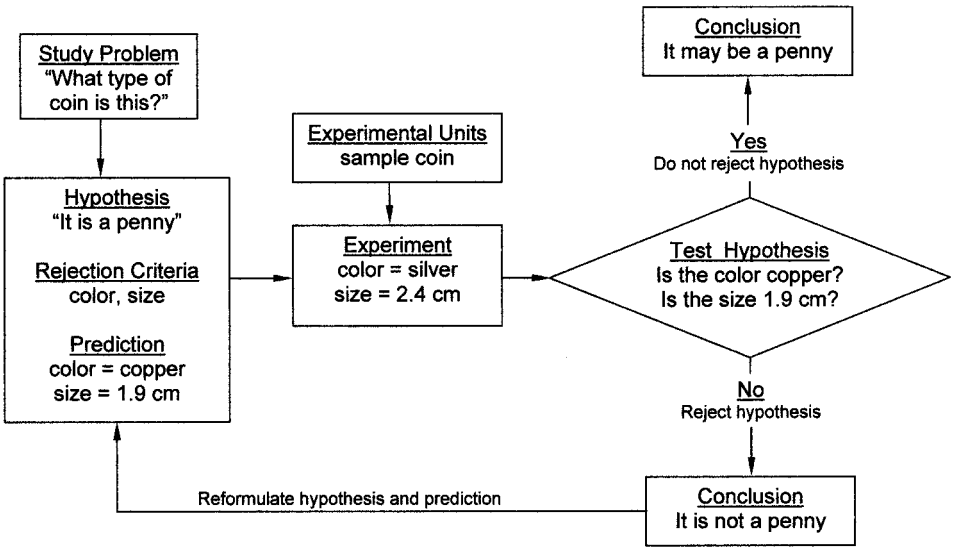

Fig. 1. Algorithm illustrating the scientific method.

To define the rejection criteria we need to specify what we should measure in the experiment. For example, we could measure the coin's diameter and color.

Make a Prediction

Next we make a prediction based on our hypothesis that specifies the rejection values. For example, we could say, "If the coin is a penny, it will have a diameter of 1.9 cm and a copper color." The rejection criteria are thus: diameter = 1.9 cm and color = copper.

Perform the Experiment

The rejection criteria determine the measurements required in the experiment. Much of experimental design is based on statistical theory that is beyond the scope of this article, but the basic idea is to determine (a) what variables to measure, (b) how the measurements should be made, and (c) what experimental units (subjects) will be used for making measurements. In our simple example we have only one experimental unit (the coin) and we need only a ruler and our eyes for making the measurements.

Test the Hypothesis

It is the hypothesis, not the experimental subject, that is being tested (despite that we say things like "The patient was tested for cystic fibrosis."). The hypothesis is tested by comparing the experimental data to the rejection criteria. In practice, this comparison is done mathematically, using a statistical procedure appropriate for the specific type of measurement data and hypothesis. If the data contradict the prediction we made, then the hypothesis is rejected. We then go back and make another hypothesis and another prediction based on the rejection criteria (we may even choose new criteria). If the data agree with the prediction, the hypothesis is accepted as possibly true, with the understanding that data collected in the future may prove it false. For example, suppose the diameter of the coin is 2.1 cm and it is silver. Obviously, we would reject the hypothesis that it was a penny. We would then create a new hypothesis (perhaps that the coin was a dime) and a new prediction (based on the diameter and color of a dime).

But suppose the diameter is indeed 1.9 cm and the color is copper. Does that prove it is definitely a penny? What if there is a foreign coin that has those characteristics? There is no way to discriminate between the foreign coin and a penny based on our simple rejection criteria. So we simply acknowledge that we may be wrong, but until we have further information we will suppose the coin is a penny. This example shows that we can do everything right in terms of following the scientific method and still end up with a wrong conclusion. It also shows how critical it is to select the right rejection criteria and make accurate measurements. You can now appreciate how science usually produces more questions than it answers.

Steps in Conducting Scientific Research

I will now expand on the scientific method to give an overview of the entire process of conducting a research project.

Develop the Study Idea

The first step is to develop your ideas about the study problem and the specific hypotheses. Ideas come from everyday work experiences, talking with colleagues, and reading professional journals. You must also consider the experiment's *feasibility*. A great project that you do not have the resources to finish is a waste of time.

Search the Literature

An important step in the research process is a thorough search of the literature. By the literature search you determine what is already known about your subject and learn about methods you might use for experiments.

Consult an Expert

Before you begin writing the plan for your project, discuss your ideas with someone who has experience with research and statistics. Advice at this point can help you refine the study question, identify appropriate experimental methods, and develop an implementation plan.

Design the Experiment

Three basic study designs are commonly used in respiratory care: the case study, the device or method evaluation, and the original clinical study.

The case study describes a particular patient care episode that has exceptional teaching value. There is usually no need for statistical analysis in a case study, so the case study is a good choice for the novice researcher.

A device or method evaluation has at least some descriptive statistics and may involve hypothesis testing to determine the efficacy of a treatment or compare the performance of a new device/method that of an older device/method. Device/method evaluations are more complicated than case studies, but they are very popular among new researchers, because they usually do not involve the complications and expense of studies that involve patients.

A clinical study is the most advanced type of study; it involves obtaining IRB permission, sophisticated statistical procedures, medical equipment, patient care, and various other complications. Clinical practice is based on this type of research. You should not attempt this type of research until you have some experience and a good mentor.

Write the Protocol

A brief but detailed research protocol serves as a set of instructions for investigators. It also serves to communicate your plans to others, such as those from whom you must obtain cooperation or permission to conduct the study.

Obtain Permission

Before conducting a study you need permission from your immediate supervisor and from any others who will be affected (eg, physicians, nurses, staff, lab personnel). If the study involves human or animal subjects, the research protocol will have to be approved by the IRB. If your study involves medical treatment of patients (or even animals), you will probably have to get a physician to act as principal investigator to obtain the IRB's permission. In addition, such studies require written consent from the study subjects or their guardians. The decision to participate in a study must be voluntary and the subject must be allowed to withdraw at any time without penalty.

Collect the Data

The best-laid plans often fall apart during implementation. Often data collection requires more time than originally anticipated. Often the protocol must be revised as problems occur. When planning for the study, make sure you consider how data will be collected, what forms will be used to record the data, and who will be responsible for the data.

Analyze the Data

Once the data collection phase is completed, the data are summarized in tables and graphs, using basic descriptive statistics. The study design may require formal statistical procedures to test the hypothesis. Finally, you must interpret the findings and form your conclusions.

Publish the Findings

There is no point in doing all the work of a study if you do not communicate your findings to your colleagues, and you cannot effectively communicate them unless you write a report. And, since you are going to write them anyway, you might as well use a style recommended by one of the medical journals. The report can be as simple as a 1-page abstract for presentation at a national meeting, or as comprehensive as an original research article. If it is published, it will be preserved as part of medical history in copies of the journal worldwide.

Basic Skills Needed by Researchers

Although the respiratory care programs in some colleges give introductory classes in research, most of the researchers I have met in the last 20 years have been self-taught. With that in mind I would like to offer a brief outline for self-study. Such a course of study has 3 main components: familiarity with measurement devices, computer skills, and statistics knowledge.

Fortunately, your training as a respiratory therapist has already provided you with strong measurement skills. Most studies you might be involved with rely on measurements of familiar variables such as pressure, volume, flow, and gas concentration. One thing you may need to learn about is the concept of *measurement error* and how it can be minimized through proper calibration procedures.

It is hard to imagine anyone actually getting through the publication stage of research without having used a computer. These days, typing skills are assumed (ie, if you don't know how to type, learn now). You also need to know how to use word processing software (eg, Microsoft Word) and you must be proficient at basic technical writing. There are many books in the library that give basic information about how to be a good writer,[3–5] but I believe the best way to learn is by working closely with a mentor who has published scientific reports. Keep in mind the cardinal rule of working with a mentor: *Put your ego on the shelf*. You must be able to accept critical review of your written words, not only in the preparatory stages but also during professional peer review by the editorial board of a medical journal.

Another key idea in writing (that is seldom mentioned in textbooks) is the necessity of maintaining a logical continuity among the major sections of your report. These sections usually include the introduction, methods, results, discussion, and conclusion. The hypothesis must be described in the introduction because the hypothesis is the unifying principle for the rest of the report. The hypothesis suggests the measurements required for the study, which are described in the methods section. All measurements described in the methods section must be represented by summary data in the results section. The data in the results section provide the basis for the discussion and conclusions, which must refer back to the initial hypothesis in the introduction. Manuscripts from novice researchers often fail peer review because they broke that logical chain.

In addition to the ability to use word processing software, I have found it very useful to be familiar with spreadsheet software (eg, Microsoft Excel). Spreadsheets are very useful for designing data-collection forms and for organizing the data. Spreadsheets can also be used to calculate basic (and even advanced) statistics and to produce tables and graphs. Somebody has to do this and it is much quicker and less expensive if you do it yourself. If you do a lot of research, you will want to use specialized statistical software for data analysis. Such programs are very user-friendly and often have "wizards" that help you decide on the appropriate procedures to use with your data.

If you are going to be a scientist, you can't get around the need for at least a basic knowledge of statistics. Such knowledge is required, if only to communicate with a statistical advisor. Statistics is a broad and often very complicated field, but the concepts and procedures you will need for most respiratory care research are not that difficult. Table 3 shows the most important concepts. There are only a handful of statistical procedures that are common in respiratory care research (Table 4). They are most conveniently grouped by the *level of measurement* represented by the study data. The levels of measurement are *nominal* (eg, male/female, lived/died), *ordinal* (eg, a pain scale or an Apgar score), and *continuous* (eg, pressure, temperature, flow, duration). Another key concept in distinguishing statistical procedures is that of *matching*. Matched data

Table 3. Basic Statistical Concepts Important for Doing Respiratory Care Research

Variables (quantitative versus qualitative)
– Central tendency (mean, median, mode)
– Data variability (range, standard deviation)
– Measurement error, calibration procedures
– Sources of study bias
Population versus sample
Parameter versus statistic
Matched versus unmatched data
Descriptive versus inferential statistical procedures
Levels of measurement
– Nominal
– Ordinal
– Continuous

Table 4. Basic Statistical Procedures Common in Respiratory Care Research

Descriptive Statistics
Tables
Graphs
Percentages
Sensitivity and specificity
Mean, median, range, and standard deviation
Inferential Statistics (Hypothesis Testing)
Procedures for Nominal Data
– Fisher's exact test (2 groups, 2 outcomes)
– chi-square test (several groups and several outcomes, unmatched data)
– McNemar test (several groups and several outcomes, matched data)
Procedures for Ordinal Data (testing for differences between 2 groups of data)
– Mann-Whitney rank sum test (unmatched data)
– Wilcoxon signed rank test (matched data)
Procedures for Continuous Data
– Pearson correlation coefficient (for testing the strength of the association between 2 variables)
– Linear regression (for predicting the value of one variable based on the value of one or more other measured variables)
– *t* test (testing for differences between the mean values of 2 groups of data)
– Analysis of variance (ANOVA) (testing for differences among the mean values of several groups of data)

are closely related in some way, such as measurements on twins, very similar subjects, or repeated measurements on the same subject. Unmatched data are measurements from unrelated subjects.

The American Association for Respiratory Care offers a 300-page, college-level textbook titled *Handbook for Respiratory Care Research*,[6] which is a valuable resource for those interested in studying the concepts I have mentioned in this article and many of the concepts mentioned in the other articles in this issue of RESPIRATORY CARE. American Association for Respiratory Care members can download the book (in PDF format) for free at the Resources page at (http://www.aarc.org).

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Peter A Cole conducting ultraviolet experiment
with Dr F S Brackett, to right.
Experiments conducted in NIH Division of Industrial Hygiene,
(photoprint, 1940).
Courtesy National Library of Medicine

The Spectrum of Respiratory Care Research: Prospective Clinical Research

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Prospective clinical research is given the greatest weight in evidence-based clinical practice recommendations, and therefore has the greatest potential to change care and help the largest number of patients. This article briefly describes the history of government regulation of prospective clinical research, how a prospective clinical research project is developed, and how the researcher seeks project approval from the institutional review board. We also evaluate 2 published studies with regard to ethical and regulatory matters that influenced the studies. *Key words: research, respiratory care, clinical trials, institutional review board, informed consent, research methodology.* [Respir Care 2004;49(10):1165–1170. © 2004 Daedalus Enterprises]

Introduction

Prospective clinical research is given the greatest weight in evidence-based clinical practice recommendations, and therefore it has the greatest potential to change care and help the largest number of patients. Prospective clinical research is a powerful way to answer important questions about medications, equipment, or treatment approaches under real clinical conditions. Though the process of conducting and publishing a prospective clinical study can often be frustrating, the end result is a gratifying labor of achievement in the advancement of human knowledge.

All research involves risk, and protecting the research subjects is the highest priority in a clinical study. Abuses of patient trust in early research led to government regulation of research in the United States and throughout the world. Local institutional review boards (IRBs) are the foundation of research-subject protection. Respiratory therapists involved in clinical research

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Table 1. Modern History of Research Subject Protection

1944	Public Health Service Act creates United States National Institutes of Health,[1] which is authorized to award research grants to nonfederal scientists
1946	Nuremberg Code, Directives for Human Experimentation[2] establishes basic ethical principles of clinical research: voluntariness, capacity, and informed consent
1964	World Medical Association's Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects,[3] states international ethical guidelines for clinical research
1966	United States National Institutes of Health[1] establishes role of local institutional review boards in regulating clinical research
1966	United States Food and Drug Administration's Statement on Policy Concerning Consent for the Use of Investigational New Drugs on Humans[4] distinguishes between therapeutic and nontherapeutic research
1973	United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issues Belmont Report,[5] which forms basis of federal regulation of clinical research
1979	Office for Protection From Research Risks codifies federal oversight of clinical research
1991	Office of Human Research Protection[6] promulgates the "Common Rule," which unifies the policies of most federal departments and agencies that conduct clinical research

should be familiar with the ethics principles of an IRB review.

Regulating Clinical Research

Table 1 shows the key regulatory events in the history of human research-subject protection.[1–6] In 1966 the National Institutes of Health decentralized the regulatory apparatus, assigning to each individual local institution that received a National Institutes of Health grant the responsibility for obtaining and keeping evidence of informed consent from patients who participated in research studies. The National Institutes of Health mandated a review process by those institutional committees and coined the term "Institutional Review Board." Until 1991, federal departments and agencies conducted, supported, and regulated clinical research with various policies. The "Common Rule"[6] was created to unify the rules and has been adopted by all these groups except the Food and Drug Association (FDA), which has its own rules and regulations. Therefore, local IRBs are policed by 2 federal agencies: the Office of Human Research Protection, which governs federally funded studies, and the FDA, which oversees research by private pharmaceutical firms. Some studies must meet the requirements and regulations of both those agencies. The Office of Human Research Protection implements the regulations and assures that institutions that conduct human research comply with the Common Rule. Loss of the Office of Human Research Protection's approval essentially shuts down an institution's human research programs.

Role of the Institutional Review Board

An IRB has one overriding objective: to protect research subjects. It has the authority and responsibility to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction. All research involving human subjects, including medical record review, must be approved by the IRB prior to enrolling subjects.

Prior to approving a clinical study, the IRB must be certain that all risks have been minimized and that the risks are reasonable in relation to any benefits to the subject and the importance of the knowledge to be gained. This requirement is clearly stated in all codes of research ethics and is central to the federal regulations. Experimental design changes may be imposed by the IRB either to improve the science of the study or to reduce the risks. IRB review often makes the study better and safer. As a study progresses, the IRB continues to oversee the balance between risks and benefits, so all adverse events and deaths must be promptly reported to the IRB. Any deviations from the approved protocol must also be reported to the IRB. Any modifications or changes in any aspect of the study must be pre-approved by the IRB, although if the change is minor, the IRB's chair may be able to expedite approval of the change.

Designing a Prospective Clinical Research Study

A clinical study is determined to be ethical or unethical at its inception; it does not become ethical because it succeeds in producing valuable data. It should be well designed, according to sound scientific principles, and be preceded by adequate laboratory and/or animal studies. Research must be done with accepted methods; reputable scientists will not accept the results of studies done without the proper IRB approval or accepted methods.

The clinical study is a very important research design, used to assess the safety and efficacy of a new medication, device, or treatment, with human subjects, by comparing 2 or more interventions or treatments. A *prospective* clinical study observes events that occur after the study subjects have been identified. The most important clinical studies

are *controlled*, which means that one subject group receives the experimental treatment while a control subject group receives either the current standard-of-care treatment or no treatment. A controlled clinical study is ethically permissible only when there is uncertainty as to which of 2 treatments or interventions is better.

Performing *power analysis* and *sample size estimation* is an important aspect of designing a clinical study, because without those calculations the sample size may be too high or too low. If the sample size is too small, the research will lack the power and precision to reliably answer the study question. If the sample size is too large, time and resources will be wasted, often for minimal gain.

Blinding

To minimize the possibility that an investigator's expectations regarding the outcome of a clinical study will bias his or her evaluation of the subject's response, an investigator may be kept unaware of which subjects are assigned to which treatment group. Similarly, a subject's hope for a cure or fear of adverse effects may cause the subject to improve or suffer adverse effects unrelated to which group he or she is in. To reduce the possibility that a subject's response will result from hopes or expectations rather than the medical interventions, it is best to have subjects unaware of whether they are in the treatment group or the control group. In a *single-blind* study the subjects do not know whether they are in the treatment or control group (but the researchers do know). In a *double-blind* study the researchers (including all health care professionals who interact with the subject) are also unaware of which patients are in the treatment or control groups. Blinding improves the validity of the study, but blinding is not always possible.

Assigning Subjects to the Experimental and Control Groups

To avoid the possibility of bias in the interpretation of results, it is preferable to conduct controlled studies by dividing subjects into at least 2 groups: those who receive the experimental treatment and those who do not (control group). To further decrease bias, the subjects are randomly assigned to the experimental and control groups, which maximizes the chance that the groups will be comparable, by eliminating the chance of bias that might occur if clinicians were to decide which patients entered which group.

Though randomized controlled clinical trails are preferred, under certain circumstances a study can use *historical controls*, meaning that either (1) the subjects' responses to treatment (or control) are compared to their own past conditions and responses to previous treatment, or (2) the controls are drawn from medical records of other similar patients who were treated in the past at the same institution. Historical-control studies are less powerful and the results may be ambiguous and contestable.

Designing the Control Group

In clinical studies the control subjects may be given either a conventional treatment, or, if none is available or appropriate, a placebo (an inactive substance made to resemble the experimental medication or an inactivated device). Placebos may be used in clinical studies where there is no known or available (ie, FDA-approved) alternative therapy that can be tolerated by the subjects. It would be unethical to give subjects a treatment that is known to be inferior to some other treatment, and such a study design would never be allowed. Similarly, it would be unethical to knowingly deny a beneficial treatment to a subject in order to conduct a randomized controlled study.

Subjects must be fully informed of the risks of joining both the control group and the experimental group. Once there is good evidence of the efficacy of an experimental treatment, it is unethical to continue to assign subjects to the control group. During the course of the study, interim analyses of the results, by the investigator or an impartial safety monitoring committee, will identify unequivocal benefits or intolerable adverse events. Usually, that analysis is performed with the group identities blinded so that only a difference between the groups can be determined. A clinical study must stop or its protocol must be modified when there is sufficient evidence of either a beneficial therapeutic effect or unacceptable adverse effects.

Selection of Research Subjects

The process of selecting the appropriate subjects for a clinical study involves several factors, including requirements of the study design, susceptibility to risk, likelihood of benefit, practicality, and considerations of fairness. It is important to ensure that the benefits of the study are distributed fairly. But it is also morally acceptable for the burden of research (ie, the risks) to fall on those most likely to benefit from the research.

Under the Common Rule some research subjects are considered vulnerable to coercion or other inappropriate influence to participate; they are more likely to be willing to accept risks in the hope that they will benefit from an experimental treatment. Vulnerable subjects are not excluded from studies solely on the basis of their vulnerability, but the IRB rigorously evaluates the risks and benefits of studies in which vulnerable subjects would be asked to participate. If more than minimal risk is involved, some degree of benefit is usually required.

Cognitively impaired, traumatized, critically ill, and comatose patients are considered vulnerable because of their

serious conditions. In addition, they may not be able to fully participate in the informed consent process, and the investigator must assess each subject's capacity to consent. If the subject is considered incapacitated, his or her legal representative may decide whether to give informed consent.

Another vulnerable population is children. Though parents are legally authorized to consent for their children, with older and/or mature children, assent should be sought. Pregnant women are also considered vulnerable, but there must be a valid basis to categorically exclude pregnant women from a study, especially a therapeutic study.

Assessment of Risks and Benefits

A clinical study may directly benefit the subjects, or the study may be of no benefit to its subjects but the study results may help others later or contribute to the advancement of scientific knowledge. A study that will not yield valuable data is unacceptable. A study should not be undertaken unless the risks are believed to be predictable, minimized, and proportional to the expected benefits. Risks include the possibility of physical, psychological, sociological, or other harm from participating in the study. Some studies are unsupported and the subject may be responsible for the costs of participating, including laboratory tests and medications. If a patient's insurance refuses to cover experimental treatment, there could be extensive economic risks for the subject. In research involving an intervention expected to provide direct benefit to the subject, a certain amount of risk is morally justifiable. In studies evaluating therapies for life-threatening illness, such as malignancy, the risk of serious adverse effects and even death may be acceptable. In research where there is no direct benefit, the investigator and the IRB must evaluate whether the risks are morally acceptable. There is a limit to the risks society can ask individuals to accept for the benefit of others.

Though financial incentives for subjects cannot be considered a benefit, subjects are often financially compensated for their time and discomfort. Such incentives must be reasonable and based on the inconveniences of the study. Excessive financial incentives are coercive and can impact the voluntariness of subjects from disadvantaged socioeconomic groups.

Informed Consent

The concept of informed consent is at the heart of research-subject protection. Informed consent is a *process*, not just a form. Information must be disclosed to enable subjects to voluntarily decide whether to participate. The informed consent procedure should be designed to educate the subject in terms he or she will understand. Therefore, informed consent documents must be written in "lay language." Medical jargon and technical terms must be clearly explained.

The Office of Human Research Protection requires that the following information be provided to subjects before they consent to participate in a study:

1. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, and a description of the procedures to be followed. The consent documents should describe the overall experience the subject will have and explain the research activity and the fact that the research is experimental.
2. A description of any reasonably foreseeable risks or discomforts the subject will experience while participating. These risks must be described separately from the risks that the subject would have from therapies they might undergo even if not participating in the study.
3. A description of any benefits to the subject.
4. A disclosure of all the possible alternative treatments and what is known about their efficacy and safety.
5. A statement describing the extent to which confidentiality of records identifying the subject will be maintained.
6. An explanation and description of any treatments the subject would receive if injured by participating in the study, and what compensation the subject would received in case of a research-related injury.
7. An explanation of whom the subject should contact with questions about the research, the subject's rights, or a research-related injury.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

Examination of a Respiratory Care Clinical Research Project

With the above background information and an understanding of the necessity of ethical conduct of clinical research, we will now review an actual respiratory care clinical research project and identify the key issues in its development and publication. One of the more important recent advances in respiratory care was the determination that respiratory-therapist-driven protocols hastened weaning from mechanical ventilation and improved certain other patient outcomes. In 1996 a randomized, controlled study[7] was published that demonstrated that daily screening of weaning readiness and performance of spontaneous breathing trials (SBTs) by respiratory therapists were more efficient than physician judgment in liberating patients from mechanical ventilation. Though these study results are familiar to most therapists, the development and conduct of

the study gives a good example of the process of scientific research.

The study involved daily evaluations of intubated patients in medical intensive care and cardiac care units. All subjects were screened for weaning readiness and then randomized into 2 groups. Subjects randomized to the experimental group underwent an SBT. If the subject passed the SBT, the physician was notified orally and a note was placed in the subject's medical record indicating the success of the SBT. The daily weaning readiness evaluations and SBTs were carried out by members of the research team not involved in the subjects' care decisions. Subjects randomized to the control group were screened for weaning readiness, but no SBT was performed.

The results were as follows: notifying the physician of the SBT success hastened successful weaning by 2 days, shortened the duration of mechanical ventilation by 1.5 days, and reduced by half the complications related to mechanical ventilation (Table 2 and Fig. 1). Costs were also significantly less in the experimental group.

The study was approved and overseen by the hospital's IRB, and informed, written consent was required and obtained from all subjects, though the report does not make clear exactly how it was obtained. Given that the subjects were intubated and possibly receiving sedative drugs, many of them must not have had the capacity to give consent. They would have been considered highly vulnerable to coercion and inappropriate influence to participate because of how ill they were. Presumably, the investigators obtained consent from each patient's legal representative (eg, next of kin), but that is not stated in the report, and should have been.

To interpret the importance of clinical research the investigators must address the potential for selection bias. The phrase "intent to treat" means all the patients who had the condition(s) that qualified them for preliminary consideration to participate in the study (ie, "the patients we intended to treat in this study"). Patients who had the qualifying conditions but did not enter the study should be compared to those who did, to identify differences between those groups and thus identify potential biases. Patients who entered but failed to complete the study must also be described. If there was a systematic exclusion of certain types of patients, that must be detailed in the report and taken into account by any reader considering using the experimental treatment in his own clinical practice.

Table 2. Outcomes in a Study of a Respiratory-Therapist-Driven Ventilator-Weaning Protocol

	Experimental Group (*n*)	Control Group (*n*)	p
Weaning days (median)	1	3	< 0.001
MV days (median)	4.5	6	0.003
ICU days (median)	8	6	0.17
Hospital days (median)	14	15.5	0.93

MV = mechanical ventilation
ICU = intensive care unit

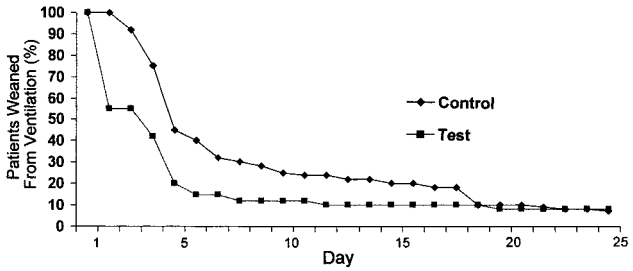

Fig. 1. Percentage of intensive care and cardiac care unit patients (in 2 study groups) weaned from mechanical ventilation. Subjects in the control group were screened for weaning readiness, but no spontaneous breathing trial (SBT) was performed. Subjects in the test group received care per a protocol (driven by respiratory therapists) that included SBT and informing the attending physician of the SBT results. Test group patients were weaned and extubated faster.

Many journals now require that the report include a flow chart that shows how many patients underwent initial screening, how many were excluded from the study and why, how many of what types of patients were included (eg, male vs female), and the various steps at which patients exited or completed the study. In our example study, 323 patients were screened, and of those 15 could not consent and 8 refused to participate (Figure 2). It appears that all patients who entered the study were either extubated or died.

The protocol for the control group in the example study did not prevent control-group subjects from receiving an SBT. If the physician decided to perform an SBT (as many undoubtedly did prior to extubation), it was performed

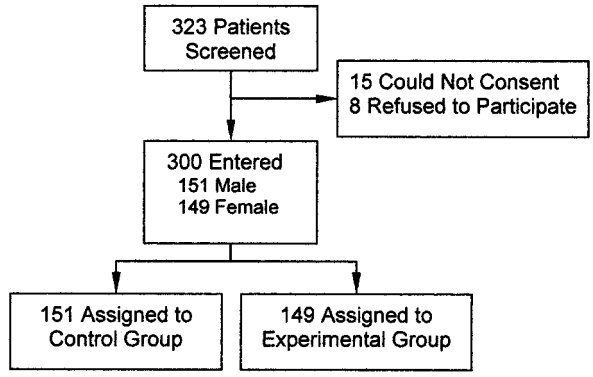

Fig. 2. Flow chart showing how many patients were screened, excluded from (or refused to participate in), and entered into the arms of the study. There were 343 "intent to treat" patients, which are the patients who met the initial study criteria (in this case, intubated patients in medical intensive care and cardiac care units).

when requested. This was probably because the investigators and the IRB would not allow denying a known, beneficial therapy. Unfortunately, the results of SBTs in the control group were not included in the report. Several questions about the experiment's design remain to be answered in future investigations. Is passing an SBT adequate to predict extubation readiness or is it passing the SBT that is the essential part of shortening weaning? Were the differences observed due to the control subjects not yet being ready to extubate at the time the successful SBT was observed in the experimental group? What form of notification was important: the note in the chart or the call from the respiratory therapist? Additional studies have shed some light on these questions.

Respiratory therapists participated in various ways throughout the study. They collected the necessary data for the weaning readiness screening. They explained the SBT to the subjects and encouraged them during its application. They monitored the subjects and reported SBT successes, failures, and concerns to the physician investigators. They reinstituted mechanical ventilation following the study and kept the results confidential even from the treating physicians until the notification occurred.

In the study described above, written, informed consent was required. For some clinical trials an IRB will waive the requirement to obtain written consent. In our study[8] of an innovative (but FDA-approved) heat and moisture exchanger with patients following cardiac surgery, the IRB waived the requirement for written consent. The studied device used a chemical reaction to convert exhaled carbon dioxide to water and heat. Bench tests suggested the device was very effective at maintaining a high humidity in inhaled gases. We designed a prospective, controlled study for a group of patients who might benefit from the added heat production—those who were hypothermic on admission to the intensive care unit following cardiopulmonary bypass. The study could not be blinded, because the devices are identifiable by appearance. However, the subjects were randomized to receive either a conventional or the investigational heat and moisture exchanger, and the data were collected prospectively. After discussions with the chair of the local IRB, the protocol was approved with a waiver of written consent. The IRB required only that the study subject's attending surgeon had to orally agree for their patient to participate in the study. Subjects were randomized and certain data elements were collected simultaneously with treatment delivery by the respiratory therapists.

Summary

In prospective clinical research several important steps are necessary. As with all research, development of the hypothesis is essential. The hypothesis develops from a clinical question and from reading other studies on the topic. Refining the hypothesis to a statement that is possible to answer as "yes" or "no" will make data analysis easier. The hypothesis statement should lead to designing a control group to be compared to the experimental treatment group. Involving an expert* in statistical analysis at an early stage will avoid difficulties when the study's data-collection is complete and conclusions are being sought. Once the hypothesis is refined and the research treatment protocol developed, the IRB must be asked for approval. If informed consent is needed, the IRB will carefully scrutinize the specific details of wording and risks. It is unlikely that your first attempt at an informed consent document will be accepted by the IRB. Do not despair; eventually an acceptable consent form will be developed.

If the above description of the process of developing and seeking approval for a clinical study is not too daunting, then you are ready to get involved in clinical research. Begin by working on someone else's project. Help obtain consent and collect data. Participate in the discussions about how to carry out a project. Listen to and offer suggestions when things are at a "bottleneck." Get a mentor to help with your first project. Clinical research is fascinating and enjoyable, and your participation in it may improve care for many people. Clinical research is an honor and a responsibility for the exceptional clinician.

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* The "expert" does not need to be a statistician, but simply someone who has done enough research to have a good understanding of statistical methods. If your study protocol is complicated, a statistician at this stage may save time and money in the long run by simplifying and clarifying what data are to be collected.