

The Spectrum of Respiratory Care Research: Prospective Clinical Research

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Summary

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 recommen-

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dations, 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

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 re-

search 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 trials 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 lan-

guage." 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 receive 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 study⁷ 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 be-

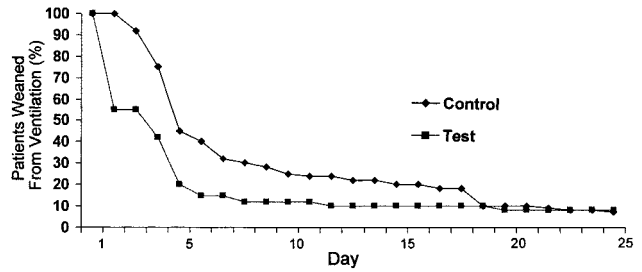


Fig. 1. Percentage of intensive care and cardiac care unit patients (in 2 study groups) weaned from mechanical ventilation. Subjects in the control group were screened for weaning readiness, but no spontaneous breathing trial (SBT) was performed. Subjects in the test group received care per a protocol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

tween 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.

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

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

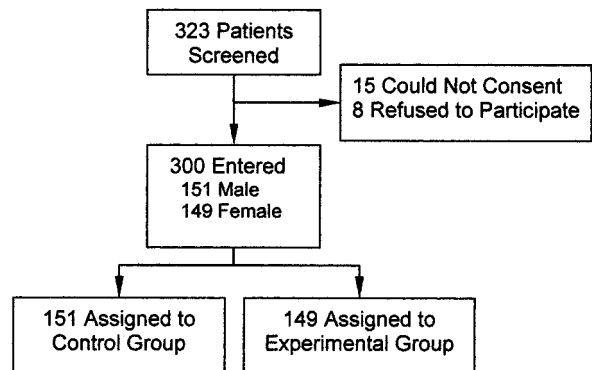


Fig. 2. Flow chart showing how many patients were screened, excluded from (or refused to participate in), and entered into the arms of the study. There were 343 "intent to treat" patients, which are the patients who met the initial study criteria (in this case, intubated patients in medical intensive 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 reinstated 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 study⁸ 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.

REFERENCES

1. A short history of the National Institutes of Health. Available at <http://history.nih.gov/exhibits/history/index.html>. Accessed July 23, 2004.
2. Nuremberg code, directives for human experimentation. Available at <http://www.nihtraining.com/ohsr/site/guidelines/nuremberg.html>. Accessed July 23, 2004.
3. World Medical Association declaration of Helsinki, ethical principles for medical research involving human subjects. Available at <http://www.nihtraining.com/ohsr/site/guidelines/helsinki.html>. Accessed July 23, 2004.
4. Code of Federal Regulations, Title 21, Parts 50 and 56, Food and Drugs. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm>. Accessed July 23, 2004.
5. Protection of human subjects; Belmont Report: notice of report for public comment. Fed Register 1979;44(76):23191-21197.
6. The Common Rule (Code of Federal Regulations, Title 45 Part 46, protection of human subjects. Available at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>. Accessed July 23, 2004.
7. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996; 335(25):1864-1869.
8. Broach SD, Durbin DG Jr. A randomized, controlled, clinical trial of a chemically-reactive heated humidifier. Respir Care 2001;46(1):37-42.

* 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.