



Innovation Versus Research: Guidelines, Concepts and Procedures for Differentiation

Guidelines

The President's Commission on the Protection of Human Subjects defines **research** as "an activity designed to test a hypothesis, permit conclusions to be drawn and thereby develop or contribute to generalizable knowledge. By contrast **practice** refers to "interventions that are designed solely to enhance the well-being of a patient". These two definitions are not mutually exclusive but they provide a context for differentiating between research and innovative therapy/procedures.

The Committee on Clinical Investigation (CCI) is charged with the responsibility of reviewing research that is conducted on human subjects. Although the distinction between innovative treatment may also be blurred in other medical disciplines, surgery is the discipline where the distinction between research and innovative therapy is most challenging. Over the past year, the CCI has held a series of discussions with members of the departments of surgery to try to clarify what constitutes research in surgery and surgical subspecialties.

This document offers some guidelines regarding differences between research and innovative therapy, suggests procedures for recognizing and documenting innovative therapies and it proposes one approach to the oversight of high-risk innovative therapies.

The goals rather than the newness of the procedure are one important criterion for distinguishing between research and innovative therapy. It can be argued that the physician's intent when proposing the therapy/procedure is central. However in most cases it is difficult to assess the physician's intent objectively because interventional research may benefit the subject while standard clinical care can yield generalizable knowledge.

Further more, the term "experimental" may obscure the distinction between research and innovative therapy. A procedure that has never or only rarely been attempted before may be viewed as "experimental" although it does not meet the standard definition of research.

Because of the many ambiguities surrounding the distinctions, the CCI has proposed a set of guidelines and concepts that are intended to assist members of the medical staff in making a distinction as to which of their activities should be considered research and therefore should fall under the jurisdiction of the IRB. These guidelines have been reviewed and endorsed by the Surgical Executive Committee. The CCI would be grateful if the Medical Staff Executive Committee reviewed these guidelines, provided additional comment and voted as to whether to adopt the

guidelines. Such a vote should be based on the assurance that all interested staff members have had an opportunity to comment.

Application of Guidelines for Surgical Specialties

The art of surgery allows a surgeon to adapt or apply a procedure or technique for a particular clinical situation that is determined to be necessary in the interest of the patient. The proposed guidelines in no way imply that this type of practice is to be considered or is necessarily research and subject to IRB review. Rather, the guidelines are intended to help the surgeon and other practitioners differentiate between use or modification of a procedure and activities that are primarily or initially performed to advance the science of surgery or a discipline for a particular procedure or set of procedures that meet the standard criterion of clinical research.

Defining Research

The Purpose of research is to seek new knowledge to restructure or reorganize existing bodies of information, to verify extant theory or to apply existing knowledge to a new situation. Research may be characterized by one or more following principles:

- Systematic investigation including research development, testing and evaluation designed to develop or contribute to generalizable knowledge.
- An activity designed to test a hypothesis that permits conclusions to be drawn, and thus contributes to generalizable knowledge.
- An objective and formal procedure is applied to obtain a directive and answer an operationally defined question.
- The systematic design that is formulated in advance and utilizes an objective approach that has the potential for yielding generalizable knowledge
- The outcomes of research increases current knowledge, scientific understanding and may not have direct practical applications.
- Interventional research may be characterized by an intervention designed to determine safety and efficacy of a interventional or diagnostic method. Besides contributing to generalizable knowledge, the procedure/intervention may offer benefit to the patient. While interventional research offers potential benefit to the patient, there is at the same time the intent to collect data that will address scientific questions.
- Generalizable knowledge includes theories, principles or relationships that can be corroborated by scientific methods of observation, experiment and inference.

Procedures and therapies that are determined to be research require review by the Committee on Clinical Investigation before they are implemented

Defining Innovative Therapy

Innovative therapy occurs when a practitioner proposes to use a treatment, procedure or intervention in a way that deviates from commonly accepted practice in a clinical encounter

Innovative therapy can be characterized by one or more of the following principles:

1. A non-standard treatment or approach that is used solely to attempt to enhance the well being of an individual patient.
2. A change from a currently accepted practice by the medical community that is based on scientific observations and explicit rationale.
3. The modification of commonly accepted procedures in small incremental steps
4. Whenever innovative therapy differs significantly from routine practice, it should be viewed as experimental. In all such cases the need to evaluate the therapy/procedure by a scientifically sound methodology under a formal research protocol should at least be considered although the fact that the procedure is novel does not automatically place it in a category of research. However, when new procedures are used repeatedly, they should be made the object of formal research at an early stage, in order to determine whether the innovation is both safe and effective

The term innovative therapy covers a large spectrum of situations. It may include a minor modification to an established procedure or a new interventional approach for a particular patient. When a proposed innovative therapy/procedure

- represents a significant increase in risk, above the alternative approaches could have been offered or
- when the procedure is so novel that the risks and benefits are unknown, it is recommended that the medical staff follow the procedures outlined below.

In ambiguous cases, members of the medical and surgical staff who propose to implement novel procedures should consult with their Department Chair or Division Chief to determine whether the proposed innovative therapy/procedure requires oversight by an independent professional. Any procedure that is determined not to require oversight should proceed in accordance with generally accepted departmental policies and practices

Oversight Procedures for Innovative Therapy Meeting Criteria I or II

In cases where it is determined that innovative therapy falls within category I or II and therefore requires oversight, the following steps should be taken under the direction of the Chairman or Division Chief.

1. Two or three medical staff members of the department should conduct an independent peer review of the patient specific proposed therapy/procedure. These individuals must not be affiliated with the patient care team and must not be involved with the performance of the innovative therapy/procedure. The review must conclude that the proposed innovative therapy/procedure is a reasonable approach, given the patient's clinical situation and the alternatives available. The peer review group must also be assured that all steps are taken to assure patient safety and a favorable outcome. A written statement should be prepared that the group agrees with the proposed procedure or therapy.
2. A separate written informed consent document containing a complete description of the procedures, risks, benefits and alternatives must be developed specific to the patient and procedure. This form should be completed in addition to the hospital's general consent forms. In addition to the actual consent form, plans should be discussed for the process of obtaining consent (who will speak with the patient, when, where ,etc.)

Although the IRB will not participate in determining which innovative procedures require oversight, the administrative office for the Committee on Clinical Investigation (CCI) will review and approve the informed consent document for innovative therapy that falls under category I or II above. The office will also provide consultation on other issues related to patient protection, whereas the recommendation for implementation of the procedures, their oversight and outcome monitoring will be the responsibility of the Departmental/Division Chairs.

3. A letter documenting the peer review process, decision and a copy of the proposed consent, including who will obtain consent, must be submitted to the CCI administrative office. If the Department Chair is not part of the peer review process, he/she should also sign the letter. The staff of the CCI and the Chairperson will review and approve the consent document as soon as reasonably possible. This review will also consider the process by which informed consent is obtained, to assure that the patient and family are adequately informed about the procedure before granting consent. The CCI will only approve the consent and will not be responsible for approving the performance of the procedure. In addition the CCI office will maintain records of the peer review and consent documents.
4. The Department/Division Chairpersons remain responsible for approving the therapy/procedure and for monitoring the outcome. The decision as to whether the procedure therapy proves useful and should be attempted again remains the responsibility of the Chairperson. Approval is only given for one patient at a time.
5. If the CCI Chairperson notes multiple submissions of the same innovative therapy, the chairperson will contact the medical staff member performing the therapy/procedure and the department/division chairperson to discuss whether a research protocol should be submitted or whether there are other mechanisms appropriate for the continued use of the therapy. It is also possible after adequate experience is gained with the procedure/therapy that the innovative therapy becomes accepted standard clinical care. This decision will remain the responsibility of the department/division chairperson.

Example Illustrations

To better illustrate the application of these concepts to actual situations, three different cases have been analyzed taking into consideration the concepts provided above.

Illustration of Research

Extensive animal testing has demonstrated that a new technique that involves an implant made of autologous chondrocytes suspended in a biodegradable alginate hydrogel can correct vesicoureteral reflux in children without the need for an invasive open surgical procedure. The procedure is performed endoscopically. This procedure has only been attempted in animals, however there is sufficient data and rationale for moving this into human subjects. Since vesicoureteral reflux is a pediatric condition, it must also be attempted in children first. Children will have a biopsy of cartilage removed from their ear. It will be cultured and expanded until adequate chondrocytes are achieved. The material will then be implanted through endoscopic guidance with the patient under general anesthesia.

Analysis:

1. The procedure has never been attempted before in humans, yet there is scientific rationale and data from animal studies to suggest human studies are appropriate to pursue.
2. The intent of this activity is to establish techniques and volumes for chondrocyte implantation. In addition, criteria for evaluating effectiveness will be refined and estimates of safety, effectiveness and resource utilization will be collected. Collectively these activities are a systematic investigation designed to contribute to generalizable knowledge.
3. These activities may be characterized as "interventional research". In addition to contributing to generalizable knowledge it may offer benefit to individual patients.
4. Although other tissue engineering practices have become accepted standard therapy (Knee cartilage procedures), at this point in time, the proposed procedure has not been generally accepted by the surgical community and is more than an incremental step of an established procedure.

Illustration of Innovative Therapy with Oversight

An ultrasound image of an individual fetus diagnoses a pulmonary mass. The mother is experiencing polyhydramnios as a complicating feature which is thought to be related to an esophageal obstruction secondary to the mediastinal mass. There is also an obstruction in of the baby's left mainstem bronchus, which has produced distention of the fetal lung and compression of the contralateral lung. These clinical features place the fetus at extreme risk at the time of separation from placental circulation. A fetal exit procedure is proposed. At the time of c-section delivery the placental circulation will be preserved until a bronchoscope is obtained. If no safe and effective conventional respiratory support is possible, the baby will be placed on ECMO prior to removal from placental circulation.

Analysis:

1. The intent is to treat one individual patient for Purposes of obtaining the best chance of preserving life. Exit procedures (manipulations of a fetus prior to discontinuing placental circulation) have been previously performed, especially in situations of airway obstruction.
2. ECMO support is also a current accepted standard of care for infants with respiratory failure in the newborn period when conventional therapy is not effective.
3. The "innovative" approach is the combination of therapies at the time of delivery. The proposed procedure is based on a combination of accepted practices by the medical community based on scientific observation and rationale.
4. This procedure involves risks to both the fetus and the mother. In particular there is a significant increase in risk to the mother above the alternative approaches of delivery.

Illustration of Innovative Therapy without Special Protections

A plastic surgeon creates a myocutaneous flap. During the creation of the flap, one of the feeding vessels is accidentally damaged. The plastic surgeon at this time sees

himself faced with two options. The first is the abandon the use of the flap which has been created or to try and salvage the flap in any manner possible. The surgeon notices that if the flap is extended slightly, an extra vessel may be able to supply circulation to the flap. However, this particular vessel has not been used previously in this type of procedure. After measuring the flap and assessing the vascularity requirements, the surgeon is able to determine that this maneuver would most likely salvage the flap and the procedure. The surgeon proceeds. After the procedure it was noted that the use of the extended flap and alternative vessel, resulted in better tissue healing and vascularity to the region. Based on this modification, the surgeon decides to perform future procedures in this modified manner.

Analysis

1. The circumstance was unanticipated and was performed solely to attempt to enhance the success of the surgery for one individual patient.
2. The procedure was a change from a currently accepted practice by the medical community based on previously established scientific observation and rationale.
3. Additional oversight of this innovative procedure is not required because it does not present risks that are so novel that they are unknown or present a significant increase in risk when compared to the previously used alternative approach.
4. Future use of this procedure is not research because its use will not be a systematic investigation designed to contribute to generalizable knowledge but could benefit from being made the subject of a research study as early as possible. There is no hypothesis and there is no objective or formal procedure to answer a question.

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