

**Lecture**

***Determining When a Clinical Activity Should be Classified as Research Requiring Institutional Review Board Review***

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**ABSTRACT**

The boundary between therapy and research may at times be difficult to distinguish, and it is, therefore, important for health care professionals to recognize when a clinical activity should be properly classified as research. Research may be subject to federal regulations which require advance review and approval by an Institutional Review Board (IRB) in order to protect the rights and welfare of patients who serve as human subjects. This paper will discuss the criteria health care professionals can use to distinguish between therapy, innovative therapy, and therapeutic or clinical research.

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## INTRODUCTION

The Institutional Review Board (IRB) is a federally mandated review body charged to "protect the rights and welfare of human subjects involved in research." This is accomplished primarily by prior review and continuing review, no less often than annually, of human subjects research. In many settings, the meaning of this responsibility is clear. However, in clinical medicine, especially that performed in the setting of an academic medical center, the boundary between therapy and research is sometimes blurred. This paper is designed to help health care professionals determine when an activity should be classified as research which, in turn, requires IRB review and approval before the project can be initiated.

## THE FEDERAL DEFINITION OF RESEARCH

"Research" is defined by the Department of Health and Human Services (HHS) regulations for the protection of human subjects as "a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge" [45 CFR 46.102(d)] (1). The Belmont Report produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research offers further clarification by stating "research designates an activity designed to test an hypothesis, permit conclusions to be drawn and thereby contribute to generalizable knowledge" (2).

These definitions, then, address both the process (a systematic investigation) and the intended result (contribute to generalizable knowledge). An activity must satisfy both criteria to be considered research. A contribution to generalizable knowledge which does not result from either a prospective or retrospective systematic investigation is not research (e.g., a case report), nor is a systematic review of retrospective data performed for quality control.

Food and Drug Administration (FDA) regulations for the protection of human subjects use a different but comparable definition of research by defining a "clinical investigation" as "any experiment that involves a test article and one or more human subjects..." which must meet the requirements of the Federal Food, Drug, and Cosmetics act. A test article is any drug, device or biologic subject to regulation under the act. The FDA goes on to claim that "the terms 'research', 'clinical research', 'clinical study', 'study', and 'clinical investigation' are deemed to be synonymous..." [21 CFR 56.102(c)] (3).

In the clinical setting, it is often helpful to classify research as either non-therapeutic or therapeutic. This classification is based on whether or not the investigation offers the subject the prospect of receiving a health related benefit.

## NON-THERAPEUTIC RESEARCH

Non-therapeutic research is research that has no intent or

purpose of producing a diagnostic, preventive, or therapeutic benefit to the subject. An example of non-therapeutic research performed in the clinical setting is a pharmacokinetic analysis of a medication. The subject may or may not be healthy, and may or may not be receiving treatment for a medical condition, but he or she is not seeking nor expecting to receive a health benefit specifically from the research. Another example would be a Phase IV post-marketing study of an FDA approved oxygenator routinely used during cardiopulmonary bypass (CPB). Such studies are designed to collect additional data on safety and efficacy which are typically used for marketing purposes. The research is considered non-therapeutic because only future patients may benefit if the blood gas exchange device under study is found to have superior performance characteristics compared to other FDA approved devices on the market.

## THERAPEUTIC RESEARCH

"Therapeutic research", in contrast to non-therapeutic research, refers to interventions that are designed to determine the efficacy and safety of a therapeutic or diagnostic method. As in the case of non-therapeutic research, the objective of *therapeutic research* is to increase generalizable knowledge (that is, to test a hypothesis and draw conclusions). However, the research is also intended to hopefully provide some or all of the subjects with a needed health benefit (that is, therapy). Though there is an intent to provide health benefit, the interventions are not applied *solely* to enhance the well being of the individual subjects who are sick (note use of the term "subject" as opposed to "patient"). An example would be a Randomized Clinical Trial (RCT) comparing the efficacy and safety of an investigational antifibrinolytic drug with placebo in CPB. While there is intent to hopefully reduce the risk of bleeding and the need for blood product administration, there is also intent to collect data in order to answer a scientific question. Another example would be an RCT which compares two FDA approved drugs.

## THE DIFFERENCE BETWEEN THERAPY AND RESEARCH

"Therapy" refers to interventions that are applied solely to enhance the well being of an individual patient. The interventions are usually procedures commonly accepted by the medical community and represent the standard of care for a given clinical condition. Therapeutic research, as defined above, may consist of the same or different interventions, but these interventions are not applied solely to enhance the well being of the individual subject. Specifically, there is also an intent "to test an hypothesis, permit conclusions to be drawn and thereby contribute to generalizable knowledge."

The practice of good medicine requires the collection of data. For example, when a patient is treated with a pharmacological agent, the health care practitioner routinely notes toxic-

ity, response to therapy, as well as other measurable results. These data are primarily utilized to enhance the well being of the patient. This information will also be used by the practitioner to design therapy for the next patient with the same disease or condition. The conscious utilization of this data for the benefit of other patients does not, however, necessarily transform therapy into research. The interventions are neither a systematic investigation, nor are they intended to contribute to generalizable knowledge.

Even the systematic collection of data does not automatically convert therapy to therapeutic research. For example, clinical tools are subjected to quality assurance mechanisms which require data collection and analysis. This is simply the practice of good medicine and is not research, providing that the only intent of the activity is to improve the clinical outcome of a defined population of patients at a given institution. However, once data is collected with the intent to use the data to contribute to generalizable knowledge, then the intervention should be considered research.

In order for an activity to qualify strictly as standard therapy, the interventions, follow-up, and any concomitant subsequent data analysis must be performed solely to enhance the well being of a particular patient (or, by extension, the well being of a group of clinically similar patients). There must be *no intent* to perform a systematic investigation in order to develop or contribute to generalizable knowledge via commonly accepted avenues of information dissemination, such as publication in a professional journal or presentation at a national meeting. If, at any point during the performance of standard therapy, the health care practitioner decides that the data being collected have sufficient value that they should be analyzed within the context of a systematic investigation and used to contribute to generalizable knowledge via publication in a journal or presentation at a regional or national meeting, then standard therapy has taken on an element of research. If only existing data will be used, the activity should be classified as retrospective research. If the practitioner intends to continue to collect data for routine clinical reasons but also analyze it in order to draw conclusions which contribute to generalizable knowledge, then the activity must necessarily be classified as *prospective therapeutic research*. In summary, the boundary between standard practice and research often boils down to one of "intent". When a clinical intervention includes any intent to develop generalizable knowledge, the argument can be made that it must be designated as research.

## THE DIFFERENCE BETWEEN INNOVATIVE THERAPY AND THERAPEUTIC RESEARCH

Health care practitioners are free to innovate (that is, use a novel treatment approach) if the innovative procedure is applied solely to enhance the well being of their patient. When innovative therapy differs significantly from routine practice, it should be viewed and treated as experimental with appropriate safe-

guards in place to protect the rights and welfare of the patients (subjects); specifically, IRB review and informed consent. In order to validate innovative therapy, the innovative procedure should be subjected early on to an evaluation via a formal research protocol.

## PATIENT VS. RESEARCH SUBJECT

A patient should be considered a "research subject" from the moment he/she agrees to participate in a therapeutic or non-therapeutic study. This agreement is formalized by signing the consent form. Even though research related interventions may not be applied to the subject until some time (days or possibly even weeks) later, it is prudent to view the patient as a human subject upon documentation of informed consent. If the research protocol requires testing for eligibility (for example, blood tests or radiographs), and the testing is carried out *solely* to determine eligibility to participate in the research, the patient should be considered a subject at the time of the testing as opposed to after eligibility is established. In addition, the consent document should address the testing. If, however, the testing is standard and would be carried out regardless of whether or not the patient is a candidate for participation in research, the patient does not have to be viewed as a research subject until formal entry into the study (that is, upon signing the consent form).

## SUMMARY

Health care professionals who conduct clinical research should always be cognizant of the fact that they are in a position of potential conflict which arises because of their goal to pursue knowledge while providing a health benefit to their patients who serve as research subjects. When a patient becomes a human subject, the investigator assumes an absolute obligation to protect fully the subject's rights and welfare in accordance with all applicable HHS and FDA regulatory requirements. At a minimum, this includes review and approval by an IRB and valid informed consent.

## REFERENCES

1. Department of Health and Human Services Rules and Regulations 45 CFR 46. Federal Register 46(26 January 1981); revised 1983; Federal Register 48(4 March 1983), 9269; revised 1991 (Federal Common Policy), Federal Register 56(18 June 1991), 28003
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3. Food and Drug Administration Rules and Regulations 21 CFR 56. Federal Register 46(27 January 1981), 8975; revised 1991 (Federal Common Policy), Federal Register 56(18 June 1991),28003.