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The practice of medicine vs. clinical research: Regulatory and ethical implications for research informed consent

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Clinical research can blur the lines between research and the practice of medicine for both physician-investigators and institutional review boards (IRBs). The question faced is, "Is it research or patient care?" The key to answering this question lies in what is intended by the physician. This intent has a significant bearing on the protection of human subjects through research informed consent.

The U.S. Food and Drug Administration (FDA) bases its separation of medical practice from clinical research not on the level of risk or the potential for benefit, but rather on the doctor's "intent." Medical practice is characterized by a doctor's intent to benefit individual patients whereas clinical research is characterized by the doctor's intent to contribute to generalizable knowledge that benefits future patients.[1] Intent is the FDA's *regulatory* dividing line between the practice of medicine, which the FDA does not regulate, and research with drugs, biologics, vaccines, and devices, which the FDA does regulate, including those previously approved by the FDA and in routine use in the care of patients.[2]

The Belmont Report[3] established an ethical code of conduct in research with human subjects in 1979 after the Tuskegee Syphilis Study became widely known in the early 1970s.[4] The Belmont Report outlines three principles of ethical conduct of research: respect for persons, beneficence, and justice.[5] Federal regulations protecting the rights and welfare of human subjects are based on these principals, as are the FDA regulatory requirements for IRBs.[6]

Written informed consent is the default regulatory requirement that is intended to ensure respect for persons through investigator documentation that each subject volunteered to participate in research.[7] Only in very limited studies under FDA oversight could written informed consent be waived by the IRB.[8] However, in 2017, the FDA issued guidance allowing written informed consent to be waived or altered by the IRB for minimal-risk research (defined at 21 C.F.R. § 56.102(i)) when the waiver will not adversely affect the rights and welfare of subjects and the investigation could not be practicably carried out without the waiver.[9]

Clinical trials in comparative effectiveness research

There is no better example of the difficulty investigators and IRBs have with the FDA separation of the practice of medicine from clinical research than that of clinical trials in comparative effectiveness research (CER), also known as pragmatic clinical trials.[10] CER is intended to closely emulate medical care in order to obtain real-life data about the safety and effectiveness of approved drugs, medical devices, and other interventions in routine clinical use, referred to as standard of care (SOC) or standard therapy. Most CER falls into the categories of observational (noninterventional) research or interventional clinical trials.[11]

Clinical trials of head-to-head comparisons of SOC therapies or interventions generally take place in the clinical setting with very little research infrastructure and have broad eligibility criteria. Any patient who has a condition that would qualify for receipt of either of the treatments being compared is eligible for the study. Therefore, very large numbers of subjects are required to overcome the differences in individual responses to treatment. Obtaining research informed consent is considered one of the major barriers to conducting CER and has fueled most of the regulatory and ethical debates in the published literature.[12]

Interventional clinical trials comparing standard therapies may be submitted to the IRB through expedited review as minimal risk studies by investigators. One rationale provided is that research-related risks of the treatments are not increased over those observed in the routine care of patients. Therefore, the IRB should consider only the incremental increase in risks of the research—mainly loss of confidentiality associated with data use.[13] Investigators may request a waiver of informed consent from the IRB or submit a consent form for review that excludes risks related to the SOC interventions under investigation.[14]