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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]

Medical care vs. clinical research: The IRB's role

A critical first step for the IRB in considering the investigator rationale for a waiver or alteration of informed consent is determining whether the research study is interventional or observational using physician intent as an aid in doing so. The burden of distinguishing an interventional clinical trial comparing approved drugs, devices, or other products under FDA's purview from an observational (noninterventional) study rests squarely on the shoulders of the IRB.

Using the FDA's distinction between medicine and research, an intervention or treatment under the FDA's purview that is not prescribed by a doctor with the intent of individual patient benefit, but rather assigned by a protocol (i.e., protocolized), is clinical research.[15] Assignment may not always be through randomization;[16] physician options for subject treatment may be limited by the study design.[17] Risks associated with *each individual* protocolized intervention subjects are exposed to are, under the regulations, considered risks of the research. Expected and serious risks are to be included in the written consent form,[18] unless there is a regulatory exception.[19] This includes, as per the FDA, risks or discomforts of standard medical procedures, exams, and tests if protocolized.[20]

If an intervention is performed in the course of a doctor-patient relationship with intent to benefit an individual patient, it is the practice of medicine. Data *about* the clinical intervention is used to answer a research question, and the choices a physician has to treat the patient are not limited by a protocol. Because interventions are performed in the course of medical care of the patient, the study is observational (noninterventional). Risks associated with medical care are not considered risks of the research and are not included in the consent form.[21] Research-related risks are generally limited to those associated with data use (e.g., loss of confidentiality), and many such studies may qualify for waiver of consent if the IRB determines the study meets *all* criteria for a waiver.[22]

Medical care vs. clinical research: Subject rights and ethical implications

It has been proposed that IRBs apply a broader interpretation of the regulations to CER than IRBs apply to other research designs.[23] IRBs may hear compelling arguments from investigators that because the research involves SOC interventions, subjects *would have* or *could have* received the protocolized interventions as a patient. Therefore, the risks associated with these interventions are not research related. The basis for this argument can be found in the FDA regulations: "In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research)."[24]

Goldstein et al. aimed to understand the ethical issues in pragmatic randomized clinical trials and found the current ethical discussion is framed by the assumption that the function of federal research oversight is to protect human subjects from physical harms.[25] Because pragmatic trials commonly involve usual care interventions, there may be no increase in physical risks compared to their use in medical practice. This leads to investigator rejection of the distinction between medical practice and clinical research. Goldstein et al. conclude that it is this rejection of the "research-practice distinction" that leads investigators to question the need for research informed consent.

Goldstein et al. point out the function of federal research oversight is the protection of subjects' rights as well as preventing research harms. The authors put forth that the conventional research-practice distinction is the most protective of subjects' rights in CER because it gives subjects the opportunity for self-determination in making a decision about whether to become a research subject or remain a patient. Despite the blurring of the lines between research and medical care in CER, IRBs are obligated, under the current regulations, to apply this distinction in the review of research and to place subject rights at the forefront of their consideration about whether informed consent should be waived.[26]

What are the ethical implications for physician-investigators who minimize subject rights in the conduct of clinical research? When a physician implies or allows subjects by default to believe that research interventions assigned by the protocol are actually chosen by the physician with intent for individual benefit, that physician has breached patient trust in the doctor-patient relationship. That same physician has also breached an investigator's ethical duty to subjects—that of granting subjects the right to self-determination about whether to become a research volunteer or remain under the care of a physician as a patient. Goldstein et al. made a very similar point comparing the duty of a physician in the care of patients to the inherent conflict of interests associated with the role of a clinical investigator.

IRBs under pressure to disregard the conventional research-practice distinction in CER

Compliance professionals should be aware that IRBs regularly face pressure from investigators to reject the conventional research-practice distinction in the review of CER. IRBs may become sidetracked by the argument that SOC interventions should not be considered part of research because subjects *would have* received the treatment as a patient, based on an interpretation of 21 C.F.R. § 56.111(a)(2) .

When evaluating all clinical research, including CER, IRBs should ask instead, "Did or will subjects receive the interventions under a doctor-patient relationship with intent for individual benefit?" If this question cannot be answered by reviewing the study documents, the investigator should be consulted and asked the same question. If doubt remains, the study should be reviewed by a fully constituted and convened IRB rather than by a single reviewer under expedited review, which is more protective of subjects, investigators, and IRBs.

The Hennepin Healthcare case underscores the FDA's regulatory perspective that a protocolized intervention of drugs under its purview does not constitute the practice of medicine. The FDA issued a warning letter to an investigator that reads, in part, "You stated that an IND was not needed…because the drugs administered in these clinical investigations were not research interventions….You also stated that all of the drug products are part of the standard of care for sedation treatment."[27] FDA then goes on to state, "The use of these drug products was not 'in the course of medical practice.' FDA has long held that when an investigator limits his choices, his patients' choices, and the choices of the people working for him in the treatment of those patients, then he is conducting a clinical investigation. That is different from the practice of medicine, where the primary intent is to treat the individual patient."

In the Hennepin Healthcare case, the IRB determined, under expedited review, that *protocolized* sedation of agitated patients constituted the practice of medicine at their institution and granted waivers of consent for their enrollment into several such research studies. The details of the Hennepin case are beyond the scope of this article. However, it is a cautionary tale to compliance professionals about how the lack of regulatory training of investigators and IRBs, including its ethical relevance to the conduct of research, can result in enormous public outrage at and mistrust in the healthcare organization.[28]

What can federal agencies do to decrease the barriers to informed consent in CER?

Federal agencies could consider allowing IRBs more flexibility in the required elements of informed consent in greater-than-minimal–risk clinical trials comparing FDA-approved products used in accordance with their approved indications—and this has been suggested by others.[29] The U.S. Department of Health & Human Services 2018 Common Rule addition of a concise and focused presentation of key elements of consent at the beginning of the consent form at 45 C.F.R. § 46.116(a)(5)(i) could be useful as a model for a shortened consent form. The current regulations allow flexibility in the elements of informed consent only if a study is minimal risk. This unintentionally encourages investigators to seek loopholes in interpretation of the regulations and ironically pressures IRBs to grant waivers of consent in greater-than-minimal–risk studies.

What can IRBs do?

IRBs cannot alter the FDA regulations for informed consent but do have control over limiting the length and complexity of consent forms. IRBs, guided by compliance professionals, can assist investigators by creating short consent form templates that include all of the required elements of consent but are limited in length. If the interventions are truly standard therapies used as per their approved indications, many of the required elements may be addressed very briefly, in one or two sentences. Other innovative ideas for informed consent have been published, but most of these do not, at the current time, meet FDA regulatory standards for informed consent, and some raise ethical concerns regarding lack of transparency about the research.[30]

What can compliance professionals do?

Healthcare and research compliance professionals have a stake in the institution's ability to preserve and nurture public trust in both the healthcare and research enterprise. Risk assessment through auditing past IRB determinations in CER is a first step. Since CER is conducted in the clinical setting with little research infrastructure, compliance professionals should train healthcare staff as well as research staff on the distinction between clinical research and medical care, and in the regulatory and ethical obligations of clinical researchers. It has also been suggested that healthcare staff can aid in obtaining written informed consent to avoid excessive research costs, which could also reduce logistical difficulties in obtaining research consent in these clinical trials. The compliance professional overseeing the IRB should help create policies and procedures to guide IRB review

of interventional and observational studies. Periodic monitoring and auditing of IRB determinations will help ensure consistency with policies. Compliance professionals could consider spearheading an institutional committee of stakeholders to review CER protocols *in advance of IRB submission*. It may not be possible for some studies to be conducted the way they are designed and preserve subject autonomy as well as trust in the institution's research enterprise.

Conclusion

IRBs are often viewed by investigators as the vehicle for regulatory solutions to barriers in informed consent in CER. IRBs are obligated under *current* FDA regulations to apply the same FDA research-practice distinction and the same regulatory standards of review to CER that IRBs apply to all research under their purview. Applying a different standard of review to clinical trials comparing protocolized SOC interventions is risky for IRBs from a regulatory standpoint. IRBs should also consider that SOC may not be SOC at their institution, or may have been modified from that of routine clinical practice, and applying the same standard of review to all protocolized interventional research is most protective of both subjects' rights and safety. Finally, the FDA does not regulate the practice of medicine with approved products used for off-label purposes, but IRBs must make Investigational New Drug and Investigational Device Exemption determinations for off-label use in research. As in the Hennepin case, there may be noncompliance with these regulations if the research-practice distinction, based on physician intent, is not considered by the IRB.

IRBs do have some flexibility in their application of criteria for waiver of consent in minimal-risk studies, though they are obligated to consider subject rights as well as safety. However, IRBs do not have flexibility to reinterpret the FDA research-practice distinction. For that matter, neither do investigators whom the FDA holds responsible for their conduct of clinical research using drugs, devices, and other products under the FDA's purview, regardless of their approval status. If there are to be different regulatory standards for CER, it is up to regulatory agencies to promulgate special regulations.

It is a slippery slope to accept the rationale that the importance of any clinical research outweighs Belmont's respect for persons through informed consent without fully considering its ethical ramifications for subjects and for the clinical research enterprise. On the other hand, compliance professionals should address investigators' concerns about barriers to research informed consent in CER by working in earnest with investigators to seek innovative yet ethical solutions within the framework of the regulations. Compliance professionals involved in research should be ready to assist with education, training, auditing, and monitoring to ensure the protection of human subjects regardless of the type of research involved. Through this approach, human subject protections, as well as public trust in the healthcare and research enterprise, will be preserved.

Takeaways

- Physician intent is key in separating medical care, intended solely for the benefit of individual patients, from clinical research, intended to contribute to medical knowledge.
- The U.S. Food and Drug Administration requires institutional review boards (IRBs) to apply the same regulations to comparative effectiveness research (CER) that IRBs apply to all research, using physician intent to distinguish observational from interventional studies.
- IRBs should not be viewed as the vehicle for regulatory change in CER; only regulatory agencies can promulgate regulations.
- IRBs should consider the adverse impact on subjects' rights as well as physical harms when determining whether consent may be waived for any research, including minimal-risk research.

- Compliance professionals can use innovative methods to assist investigators in addressing the barriers to informed consent in CER while ensuring the rights of subjects are protected.

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