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What Impact Will the Shinal Case Have on Informed Consent in Clinical Research?

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Introduction

Informed consent recently made the headlines with Congress and the U.S. Food and Drug Administration (FDA) expounding on circumstances where they will accept the alteration, minimization or even outright elimination of informed consent in certain clinical research trials.[1] Some might argue that this continues the slide towards weakened protections afforded to patients and clinical study participants. However, some courts have taken to interpreting the requirements for informed consent rather strictly, especially as they apply to the performer of the informed consent process.

Background

According to the Code of Federal Regulations as applied by the Department of Health and Human Services,[2] an investigator may only involve a human being as a subject in research if the investigator has obtained legally effective informed consent from the subject or the subject's legally authorized representative. The Code of Federal Regulations, as applicable to the FDA,[3] echoes these expectations. However, FDA guidances further explaining these practices[4] allow not only the investigator, but also "other study staff" to "[conduct] the informed consent interview [with] the subject."

The FDA repeatedly states that the informed consent requirements in 21 C.F.R. § 50 do not preempt any applicable federal, state or local laws that require additional information to be disclosed for informed consent to be legally effective.[5] Instead,"[w]here the regulations differ, the regulations that offer the greater protection to human subjects should be followed."[6] This approach ensures that clinical research subjects receive the maximum protection offered under the law.

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[1] Michael Mezher, *FDA Issues Guidance on Informed Consent Waivers for Minimal Risk Studies*, Reg. Aff. Prof. Soc'y (July 24, 2017), http://raps.org/Regulatory-Focus/News/2017/07/24/28116/FDA-Issues-Guidance-on-Informed-Consent-Waivers-for-Minimal-Risk-Studies/.

[2] 45 C.F.R. § 46.116.

[3] 21 C.F.R. § 50.20 requires in relevant part that "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."

[4] *Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors*, U.S. Food & Drug Admin., https://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm (last visited July 28, 2017).

[5] 21 C.F.R. § 50.25(d).

[6] *Id.*

Who is an Investigator?

Informed consent laws and regulations apply to investigators and subinvestigators. The regulations define an investigator as "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject).[7] In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. Subinvestigators include other members of the team that perform certain significant functions.[8] Clinical research is almost always conducted by a team of individuals, typically led by the principal investigator listed on FDA Form 1572 as the "responsible leader of the team."[9] The FDA clarifies, however, that the principal investigator need not be a medical doctor and that a "physician can be a subinvestigator to perform those study functions requiring the appropriate level of medical expertise."[10] This suggests a great deal of flexibility in federal regulations and their interpretation as to who may be considered a principal investigator or a subinvestigator, and it also means that an individual who is not a physician may be delegated the primary responsibility to obtain a subject's informed consent.

In recognition of the time constraints investigators might face, FDA guidance allows "other study staff" to conduct the informed consent interview.[11] Practically speaking, this typically involves the study nurse or coordinator. Still, the regulations seem relatively clear that they expect the principal investigator to obtain legally effective informed consent.

The *Shinal* Case

Although federal guidance is relatively flexible as to how the clinical research informed consent process is to be performed, a recent court case may signal a change to a stricter model. On June 20, 2017, a divided 4-3 Pennsylvania court, speaking on a seemingly unrelated issue, interpreted the law to support the plain meaning of the regulations themselves and not the interpretation of these regulations as seen in the FDA guidance. (It is not clear whether the court was even aware of FDA's guidance or if it deemed clinical research relevant.) The case, *Shinal v. Toms*, involved a woman undergoing surgery to treat brain cancer.[12] The treating physician's assistant obtained a signed informed consent form from Mrs. Shinal prior to surgery. Unfortunately, during surgery, Mrs. Shinal suffered permanent injury from complications and sued the physician, alleging his failure to explain the risks of and alternatives to her surgery.

Until the *Shinal* case, physicians interpreted the duty to obtain informed consent as one that could be delegated to a qualified staff member. This delegation could include the entire of informed consent process, including talking with the patient, discussing the procedure in question, and then obtaining the patient's informed consent. However, the *Shinal* Court found that effective informed consent stems from the contractual nature of the physician-

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[7] 21 C.F.R. § 511.3; 21 C.F.R. § 312.3(b).
[8] 21 C.F.R. § 312.3.
[9] U.S. Food & Drug Admin., Form 1572: Statement of Investigator, OMB No. 0910-0014 (Feb. 2016).
[10] Cynthia F. Kleppinger, U.S. Food & Drug Admin., Division of Good Clinical Practice Compliance, Presentation at the FDA 2013 Clinical Investigator Training Course: Investigator Responsibilities – Regulation and Clinical Trials (Nov. 13, 2013), https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm378565.pdf.
[11] *Id*.
[12] *Shinal v. Toms*, 162 A.3d 429, 432-36 (Pa. 2017).

patient relationship and consequently requires a "meeting of the minds" between the parties, which could only occur by a physical interaction between the doctor and patient.[13] In support of its holding, the Court quoted *Kelly v. Methodist Hospital*, noting that the physician's unique relationship with the patient, as well as the physician's education and training, mean that "the physician is in the best position to know the patient's medical history and to evaluate and explain the risks of a particular operation in light of the particular medical history."[14] Further, the physician has a duty to disclose these risks to the patient.[15] Consequently, the Court held that, in the state of Pennsylvania, the duty to provide informed consent belonged to the physician alone and was non-delegable, because "obtaining informed consent results directly from the duty of disclosure, which lies solely with the physician."[16]

Implications for Informed Consent in Clinical Research

Although the *Shinal* case applied to medical practice, its reverberations can already be felt in clinical trials, where some might argue that informed consent requirements are, if anything, more stringent than for medical care.[17] A *prima facie* interpretation of the Court's opinion suggests that informed consent by the physician is non-delegable. While this reading is not any more burdensome than a strict reading of the regulations, which *prima facie* require that only the principal investigator can perform the informed consent interview, it does place an unexpected burden on clinical research facilities. Although it is unclear whether the Court intended to apply this opinion to clinical research, there is little to suggest that courts would not uniformly apply the same informed consent standards used in the medical practice to clinical research.

If this interpretation of the law applies, the Court's holding in *Shinal* will likely have a significant implication on the speed of clinical research in the face of an already time-consuming informed consent process. The Court's interpretation of this law suggests that investigators will likely need to personally engage with each potential study participant to discuss the procedure, possible alternatives, and to make all necessary disclosures.

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[13] *Gray v. Grunnagle*, 223 A.2d 663, 674 (Pa. 1966).
[14] *Kelly v. Methodist Hosp.*, 664 A.2d 148, 151 (Pa. Super. 1995).
[15] *Shinal*, 162 A.3d 429, at 453.
[16] *Id.*
[17] *See, e.g.,* Ctrs. For Medicare & Medicaid Servs., S&C-07-17, Revisions to the Hospital Interpretive Guidelines for Informed Consent § 482.51(b)(2) (Apr. 13, 2007) (suggesting the ideal content to include during the informed consent process) and compare with Food & Drug Admin., *Informed Consent for Clinical Trials*, https://www.fda.gov/forpatients/clinicaltrials/informedconsent/default.htm (last updated Feb. 25, 2016) (listing the elements of informed consent required for clinical trials). The elements of informed consent for clinical trials are more numerous than those recommended for medical treatment, and include requirements that the investigator obtaining informed consent explain any potential discomforts the subject might experience during research, the purposes of the research, potential compensation for injuries received during the trial, the subject's rights, and the voluntary nature of the clinical trial, among others. *See id.* These additional requirements are likely intended to control for the possibility of therapeutic misconception that exists in the clinical trial setting. *See* Cecilia Nardini, *The Ethics of Clinical Trials*, 8 eCancer Med. Sci. (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3894239/pdf/can-8-387.pdf.

Investigators are notoriously busy[18] and typically delegate much of the process of obtaining informed consent to qualified study personnel. However, they should, at minimum, ask the person if he or she has any questions about the study and determine whether the person is giving proper informed consent. This flexibility allows greater efficiency and smoother process flow even as the investigators' workflow grows more demanding. In fact, in some cases, the study nurse might be more knowledgeable about certain study details than the principal investigator. In addition, consent by the study nurse minimizes the chance of undue influence that is inherent in the patient/physician relationship.

Since informed consent is a time-consuming process, reserving the responsibility to just the principal investigators — who probably have the least amount of time — raises other issues about the adequacy of consent. It adds one more burden to physicians who already feel overburdened by clinical research duties and are not always available when it is convenient for the patient.

Issues with the Shinal Ruling

The court found for the plaintiff because the physician relied on a subordinate to obtain informed consent from the patient, which the court held was a duty non-delegable by the physician. This raises several issues:

First, it is not clear whether the explanation was inadequate because the physician possessed a duty inherent in his or her role to obtain informed consent, or whether the informed consent process must simply be performed by the professional in the best position to do so. In medical practice, it is reasonable to expect that the physician is the individual best-placed to discuss the clinical implications of a potential procedure. The physician will know the patient's health condition better than the other individuals participating in the procedure, will have the most experience and training in performing the patient's procedure, and will best understand the risks and alternatives.

However, informed consent in clinical studies requires a broader discussion that might need the involvement of additional team members. For example, clinical trial subjects must be informed of the possibility of compensation in the event of injury caused by the trial.[19] Although the physician might be the best individual to obtain a subject's informed consent with respect to medical procedures, other team members might need to participate in the informed consent process to ensure the patient is adequately informed in all aspects of the clinical study. If the study involves a technical procedure, an expert in that procedure might be better qualified to explain it to the subject. Similarly, the investigator might not be the best person to explain the logistics or financial ramifications of the study. In some cases, a subinvestigator might be more expert in the specifics of the medicine than the principal investigator, who might be more knowledgeable in the mechanics of clinical research. Ultimately, the *Shinal* court found that the reason the physician is in the best position to obtain informed consent is the "education, training and expertise" upon which the patient

[18] Surgeons, for example, work an average of 50-60 hours per week, not including time spent on call. *Surgical Career Lifestyle Issues,* Am. Coll. Surgeons, https://www.facs.org/education/resources/medical-students/lifestyle (last visited July 29, 2017).
[19] *See* Food & Drug Admin, *supra* note 17.

relies.[20] Requiring the physician to serve as the sole touchpoint for informed consent in clinical studies might not accomplish that objective.

Exacerbating this issue is the time span for informed consent. In medical practice, the informed consent process begins when the patient meets with his or her physician for the first time to discuss treatment.[21] However, the time span is much longer in clinical trials and does not always involve human interaction. Many human subjects protection experts assert that the informed consent process starts with the first advertisement the potential subject sees and continues through the end of a clinical study. Considering the extended time span of informed consent in the clinical trial setting and the additional procedures and issues that might arise not involving the original investigator, it is impractical to expect the investigator to manage all aspects of the informed consent process from beginning to end. Accordingly, additional team members will become involved as different aspects of the trial process call for their unique expertise.

Causing further confusion is the difference in professional designations between medical practice and clinical trials. While the *Shinal* Court refers to the "physician," the term "physician" is not synonymous with the term "principal investigator." This might cause confusion as to who obtains the subject's informed consent. As mentioned above, the principal investigator in a study might not even be a physician, so under a strict reading of *Shinal* suggesting that only a physician performing the procedure can obtain informed consent, the *Shinal* case might not apply. However, in the scenario where the subinvestigator is a physician, then *that* physician might have the duty to the patient. Under a looser reading of *Shinal,* where the person obtaining informed consent must be the individual in the best position to do so, this duty might fall ultimately on the principal investigator or on other team members, depending on their areas of expertise.

Additionally, as stated above, the *Shinal* Court found that effective informed consent stems from the personal, interactive nature of the physician-patient relationship, noting that "[w]ithout direct dialogue and a two-way exchange between the physician and patient, the physician cannot be confident that the patient comprehends the risks, benefits, likelihood of success, and alternatives [to treatment]."[22] If this ruling were to be fully applied, it could invalidate all consent obtained without a physical physician-patient interaction. While the relationship is justifiably special, there is nothing in the contractual aspect of that relationship that requires physical interaction. The success of telemedicine even argues against the need for physical interaction in the medical part of the relationship.

Additionally, if the principal investigator is in the process of explaining the study to a potential participant, it is unlikely that the court would prohibit the study nurse from interjecting a clarification or providing supplemental information. Or, if the principal investigator and the study participant cannot converse fluently in the same language, it is doubtful that the court would disallow the use of an interpreter.

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[20] *Shinal*, 162 A.3d 429, at 453.
[21] U. of Wash. Sch. Med., *Informed Consent in the Operating Room*, Ethics in Med., https://depts.washington.edu/bioethx/topics/infc.html (1998).
[22] *Id.*

Conclusion

The *Shinal* case, like many, raises more questions than it answers, especially when applied to clinical research, which does not constitute traditional medical care due to its investigative nature.[23]

Physicians conducting clinical research in Pennsylvania should obtain advice from their legal counsel, should probably be involved in the consent process if they are the principal investigator, and, in consideration of the potential demands placed on researchers regarding adequate informed consent, should certainly strive to obtain informed consent using either their physician researchers or their experts best positioned to obtain effective informed consent.

With the issues discussed above, the mere existence of the ruling invites plaintiff attorneys to argue it in other cases, even outside Pennsylvania.

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[23] *See* Nardini, *supra* note 17.