State Regulation of Pharmaceutical Clinical Trials

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I. INTRODUCTION

When conducting clinical studies in the United States, pharmaceutical companies focus their regulatory attention on the requirements imposed by the Food and Drug Administration (FDA). That "FDA-centrism" is natural, given that drug companies are obliged to comply with FDA requirements, or face rejection of their marketing application and potential enforcement sanctions. Good clinical practices (GCPs) concentrate on FDA and related international standards. Clinical trials designed to obtain international registrations must comply with many different national regulations. Yet, focusing on FDA and international regulations to the exclusion of other, more local, legal requirements can be short-sighted—and can put the sponsor at risk.

This article will discuss the importance of local regulations. It does not purport, however, to be an exhaustive survey of state laws. Compiling and updating all of the state laws relevant to clinical research is a formidable task. Nevertheless, there are a large and increasing number of state requirements that apply to pharmaceutical clinical studies. Ironically, while there has been considerable discussion about the harmonization of international standards, within the United States there appears to be increasing divergence among the states.

One area that illustrates the disharmony in the United States is informed consent. Drug studies conducted to support FDA marketing applications must comply with the requirements set out in FDA's informed consent regulations.[1] While these regulations set out the elements of informed consent required by FDA in some detail, they do not preclude the states from imposing their own requirements. Indeed, FDA's informed consent regulations specifically state that the states are not preempted from establishing additional requirements.[2]

The states have always had an important role to play in determining whether a patient had properly consented to administration of an investigational therapy. Although judicial decisions regarding claims against sponsors arising out of clinical trials are relatively rare,[3] there has been a substantial amount of litigation in state courts over the adequacy of consent by patients in other contexts (e.g., consent to medical treatment). In addition, several recent developments likely will give state requirements even greater prominence in determining whether valid informed consent has been obtained in FDA registration trials.

The increased focus on studies with pediatric populations is one factor that will enlarge the rule of state regulations.[4] Congress has adopted legislation that gives

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[1] 21 C.F.R. pt. 50.

[2] *Id.* § 50.25(c).

[3] This may change. The volume of lawsuits involving clinical research appears to have jumped significantly in the past few years, spurred by some well-publicized problems with a few clinical studies.

[4] In 1998, FDA finalized a regulation requiring drug manufacturers, in many situations, to conduct studies with children. Although the pediatric rule resulted from awareness that a majority of the drugs approved by FDA had not been tested on—or approved for use in—children and, sought to improve pediatric use information, it did not address ethical or legal issues such as informed consent. There was significant opposition to this rule by medical, industry, and consumer groups who filed suit. On October 17, 2002, a federal district court ruled that FDA did not have the authority to require or enforce pediatric studies. Ass'n of Am. Phys. & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (Oct. 17, 2002).

financial incentives to conduct studies in children. The Food and Drug Administration Modernization Act (FDAMA),[5] signed into law on Nov. 21, 1997, gives qualifying sponsors of certain new and already-marketed drugs who conduct pediatric clinical trials an additional six months of marketing exclusivity and patent protection in which they do not face generic competition.[6]

Consistent with this focus on pediatric trials, requirements for additional pediatric safeguards for children participating in FDA-regulated clinical trials resulted from the Children's Health Act of 2000.[7] The Children's Health Act required the Secretary of the Department of Health and Human Services (DHHS) to adopt provisions for the protection of children enrolled in clinical trials supported or conducted by DHHS.[8] These requirements were adopted as an interim rule by FDA and later were codified in 21 C.F.R. Part 50, Subpart D, entitled "Additional Safeguards for Children in Clinical Investigations." The focus on pediatric involvement in clinical trials is ongoing. In 2003, the Pediatric Research Equity Act of 2003[9] was enacted. This Act permits FDA to require applicants to test for and assess the safety and efficacy of new drug and biologic products in pediatric populations, where appropriate.[10]

Similarly, drug companies are conducting more studies with patients suffering from conditions that adversely affect cognitive function. Once again, the standards governing competence of a patient and the right of a third party to give consent for that patient are governed by state law and not FDA regulations.

Another area where state laws loom larger in clinical trials involves the issue of patient privacy. With the enactment of the Health Insurance Portability and Accountability Act (HIPAA),[11] the impact on issues regarding privacy need to be considered. HIPAA contains provisions protecting the confidentiality of patient identifiable medical information. These provisions, which limit the collection, use, and disclosure of medical information, apply to investigators and investigative sites. HIPAA itself has been highly publicized. Yet, although receiving less attention, states also have been regulating patient medical data. This is important because the HIPAA standards do not preempt state medical privacy law where state law is more stringent.

State laws also surface in a variety of other contexts. Most states have their own laws relating to genetic testing; a few states even have their own separate subject rights, HIV, and controlled substances laws. In addition, there exist idiosyncratic state laws, which appear to be unique to a particular state (e.g., California's law regulating the use of controlled substances in clinical trials).

Certainly, it would be easier all-around if the FDA-centric view of informed consent prevailed. Determining the applicable legal requirements, and adhering to them, would be much simpler if the validity of informed consent could be determined simply by consulting 21 C.F.R. Part 50 and the investigational new drug (IND) regulations.[12] Sadly,

[5] Pub. L. No. 105-115, 11 Stat. 2296 (1997).

[6] *Ass'n of Am. Phys. & Surgeons*, 226 F. Supp. 2d at 204. This has spurred additional clinical research in children. Although pediatric studies must meet FDA data standards, the legal standards regarding the obtaining of informed consent from children ultimately remain a function of state law, not FDA regulations.

[7] Children's Health Act of 2000, 42 U.S.C. §§ 201 et seq. Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589 (Apr. 24, 2001) (codified at 21 C.F.R. pt. 50, subpt. D).

[8] Additional Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9814 (Mar. 8, 1983) (codified at 45 C.F.R. pt. 46, subpt. D).

[9] Pediatric Research Equity Act of 2003, 21 U.S.C. § 355(c) (2004).

[10] 48 Fed. Reg. at 9814.

[11] Health Insurance Portability and Accountability Act of 1996 (HIPAA), Pub. L. No. 104-191, 110 Stat. 1936 (codified in scattered sections of 42 U.S.C. and 29 U.S.C.).

[12] 21 C.F.R. pt. 312.

while FDA's regulations are crucial, they are not the only regulatory requirements relating to informed consent or other research-related issues, thus the failure to be aware of state requirements can create legal problems (i.e., what you don't know can hurt you). This article explores some of the state law provisions that potentially affect drug companies who are conducting clinical studies in the United States.

II. PARTICIPATION BY MINORS

Drug companies regularly conduct clinical studies to support the use of medications in children. In addition, recent legislation generally requires that new drugs also be tested on children.[13] FDA's regulations require that subjects, including minors, provide informed consent prior to participating in a study.[14] An interim rule for the additional protection of children addresses the assent and consent requirements for children enrolled in clinical trials involving FDA-regulated products.[15] The final regulations were adopted in order to comply with provisions in the Children's Health Act that required additional protection for children in all research supported, conducted, or regulated by the DHHS.[16]

The final regulations require institutional review boards (IRBs) to "review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in sections 50.51, 50.52, or 50.53 and the conditions of all other applicable sections of subpart D."[17] Sections 50.51, 50.52, and 50.53 describe different factors to be considered and documented by an IRB for clinical investigations with children. For example, IRBs must determine and document whether the investigation: 1) presents more than a "minimal risk"; 2) presents more than a minimal risk, but has the potential for individual benefit to the child; or 3) presents more than a minimal risk and no potential or direct benefit to the child, but may result in increased and important knowledge of the "disorder or condition" being studied.[18] Each of these sections requires, at a minimum level, that "adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in § 50.55."[19] Where the clinical investigation involves a "greater than minimal" risk to the child, additional factors also must be considered.[20] These factors include: 1) whether the risk is justified by the benefit, 2) whether the benefit will be comparable to other available options, or 3) whether the "intervention ... [will] yield generalizable knowledge vital [to] understanding or ameliorating the disorder or condition."[21] Thus, FDA requires that permission and, potentially, subject assent, be obtained. While FDA imposes the obligation, the legal framework for determining who can give permission for a minor—or whether the subject even is a minor—remains a creation of state law.

For studies involving very young children, some of the consent issues are fairly straightforward. Very young children are not capable of giving consent, nor are they able to participate in the decision to enroll in a trial; therefore, their assent may not be

[13] Pediatric Research Equity Act of 2003, 21 U.S.C. § 355(c) (2004).
[14] 21 C.F.R. § 50.27.
[15] 66 Fed. Reg. at 20,589.
[16] *Id.* at 20,591.
[17] 21 C.F.R. § 50.50.
[18] *Id.* § 50.51-.53.
[19] *Id.*
[20] *Id.*
[21] *Id.*

needed. Permission to participate in a study must come from a parent, guardian, or other adult authorized under state law to allow the child to be enrolled in the study.

Determining that an adult does have the legal authority to provide valid permission is not always simple. If the parents have divorced, can a noncustodial parent with whom the child is temporarily staying allow the child to participate in a study? What about a grandparent who is raising a child but who has never been appointed guardian? These are issues that can be decided only by reference to the law of the state in which the study is being conducted.[22] If the person who signs the form is not a legally authorized representative under state law, the validity of the permission may be called into question.

Young children will not be able to understand the nature of a clinical study and, therefore, will be unable to provide any meaningful insight into whether they wish to participate in the study. As children grow older, they gain an increasing ability to make decisions for themselves. Thus, even if they are too young to provide informed consent to participate in the study, they may be old enough to evaluate a simplified version of the consent form and give their assent.

In their *Informed Consent, Parental Permission, and Assent in Pediatric Practice* policy statement, the American Academy of Pediatrics stresses the importance of including children and adolescents in the decisions involving their healthcare.[23] The policy identifies assent as a method for empowering children, developing trust, gaining cooperation, and possibly improving patient-physician relationships.[24] While acknowledging that there may be limitations to a pediatric patient's capacity to assent and that there will be situations that are inappropriate for assent, the policy suggests that involving children in discussions related to their healthcare generally will benefit children.[25]

FDA requires IRBs to "determine that adequate provisions are made for soliciting the assent of the children" participating in a clinical investigation; however, FDA leaves to the IRBs the determination of whether a child is capable of assenting.[26] FDA lists factors, such as age, maturity, and psychological condition as those to be considered when determining whether a child is capable of providing an assent or whether to proceed without the involvement of the child.[27] Very few states address the issue of children's assent. One exception is Illinois, which has a statute in its social services title requiring that "[a]dequate provisions ... be made for the voluntary assent of minors who are capable" in research involving children and their families.[28]

In addition to determining that provisions are made for seeking children's assent, FDA also requires IRBs to determine "that the permission of each child's parents or guardian is granted."[29] FDA defers, however, to state law to determine whether one or

[22] Other, even more complicated, situations of the type favored by law school professors are readily imaginable, such as when a noncustodial father residing in State A seeks to enroll his visiting daughter, who lives in State B, in a clinical study. Which law is used to determine the father's authority to provide consent—State A's or State B's? The answer to these types of questions is a creature of state law. And family law is almost exclusively a matter of state, not federal, law. The potential importance of the interplay between federal law and state custodial law is underscored by the Supreme Court's resolution of the challenge to the Pledge of Allegiance. Elk Grove Unified Sch. Dist. v. Newdow, No. 02-1624, 2004 WL 1300159 (2004).

[23] American Academy of Pediatrics, *Informed Consent, Parental Permission, and Assent in Pediatric Practice*, 95 PEDIATRICS 314 (Feb. 1995).

[24] *Id.*

[25] *Id.*

[26] 21 C.F.R. § 50.55(a).

[27] *Id.* § 50.55 (b)-(d).

[28] ILL. ADMIN. CODE tit. 89, § 432.6 (2003).

[29] 21 C.F.R. § 50.55(e).

both parents need to give permission.[30] Where a trial involves no more than a minimal risk, or there is risk but also the likelihood of a direct benefit to the child, one parent's signature may be sufficient, "if consistent with State law."[31] Where a clinical trial involves more than a minimal risk and no likelihood of direct benefit, but may result in important information that can be used to treat the studied condition, FDA requires permission from both parents unless "legal responsibility ... [is] consistent with State law."[32] Once again, FDA defers the issue to the states.

The importance of determining state law does not necessarily diminish when the study population involves older children. For example, the age of consent varies among states. In many states, the age of consent is eighteen, but that is not the case universally. The age of consent is sixteen in Kansas, Rhode Island, and South Carolina,[33] but in Nebraska and Alabama, it is nineteen.[34] Further complicating the issue is that the scope of the conduct to which the minor may consent differs among states. In Kansas, the sixteen-year old can consent for "medical or surgical treatment or procedures," while a sixteen-year old in Rhode Island can consent for "routine emergency medical or surgical care."[35] A sixteen-year old in South Carolina can consent "to health services other than operations."[36] Whether administration of an investigational drug is considered "routine" in Rhode Island is purely a question of state law. In Alabama, a minor who is fourteen or older, graduated from high school, married or divorced, or pregnant may consent for "any legally authorized medical, dental, health or mental health services."[37]

Introducing yet another wrinkle is that some states have emancipation laws. Under these statutes, an emancipated individual who has not yet reached the statutory age of consent is deemed to be an adult and thus capable of giving consent. An adolescent can achieve emancipation in different ways. In Michigan, emancipation may occur by operation of law or following the filing of a petition by the minor. Emancipation by operation of law occurs when the minor is married, reaches eighteen years of age, or is on active duty with the armed forces.[38]

Alternately, a minor, the minor's parent, or a government agency may request emancipation for the minor by filing a petition or application. The extent of the emancipation and the criteria for granting the emancipation differ from state to state. In Montana, a limited emancipation may be granted and the order will establish specifically what rights and responsibilities are to be given to the minor. This may or may not include the right to consent to medical treatment or research.[39] In Nevada, if a petition for emancipation is granted, the minor is considered an adult and can incur debt, establish a residence, and consent to medical treatment.[40]

There is an exception to the requirement for consent by a parent or legal guardian for medical treatment. The mature minor exception to the requirement for parental consent for medical treatment is recognized at common law. This exception is framed by the common law rule regarding capacity, sometimes called the Rule of Sevens. Under the

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[30] *Id.* § 50.55 (e)(1).

[31] *Id.*

[32] *Id.* § 50.55 (e)(2).

[33] KAN. STAT. ANN. § 38-123b (2002); R.I. GEN. LAWS § 23-4.6-1 (2002); S.C. CODE ANN. § 20-7-280 (Law. Co-Op. 2002).

[34] NEB. REV. STAT. ANN. § 43-2101 (2003); ALA. CODE § 26-1-1 (2003).

[35] KAN. STAT. ANN. § 38-123b (2002); R.I. GEN. LAWS § 23-4.6-1 (2002).

[36] S.C. CODE ANN. § 20-7-280 (2002).

[37] ALA. CODE § 22-8-4 (2003).

[38] MICH. COMP. LAWS § 722.4 (2002).

[39] MONT. CODE ANN. § 41-1-501 (2002).

[40] NEV. REV. STAT. ANN. § 129.130 (Michie 2003).

Rule of Sevens, a child under the age of seven is presumed to have no capacity to consent; a child between the ages of seven and fourteen has a rebuttable presumption of no capacity to consent; and a child between the ages of fourteen and twenty-one has a rebuttable presumption of capacity to consent. For consent to be effective, the person consenting must have the capacity to consent.[41] This "rule" is not legally binding and can be superseded by state legislatures, courts, the circumstances of individual cases, or other factors.

Even where a minor appears to have the capacity to consent, legal problems may arise. In Tennessee, an osteopath was sued by the parents of an almost-eighteen-year-old patient who had sought out and consented to osteopathic manipulation for back pain without her parent's knowledge or consent.[42] The patient had driven herself to the doctor's office alone, discussed her symptoms, relayed information regarding her diagnosis by orthopedic specialists, allowed the physician to perform the manipulation, and paid for his services with a check signed by her father.[43] She later developed complications and her parents filed suit claiming medical malpractice, battery for failure to obtain parental consent, negligent failure to obtain consent, and failure to obtain informed consent.[44]

The trial court directed a verdict in favor of the defendant on the issue of medical malpractice, finding that the plaintiff had not met a statutorily-defined burden required for medical malpractice. The jury, after receiving instructions that included information on the mature minor exception to parental consent, found in favor of the defendant on the remaining issues. The appellate court affirmed the verdict on the issue of medical malpractice, but reversed on the issue of battery. Based on its finding that neither the Tennessee legislature nor the Tennessee Supreme Court had adopted the mature minor exception, the appellate court found there was no effective consent from the minor or her parents, which meant the treatment resulted in a technical battery.

Ultimately, the Tennessee Supreme Court reversed the appellate court's finding of battery related to lack of consent, by finding that the plaintiff had the capacity to consent under the mature minor exception. In its analysis, the court, although recognizing some statutory exceptions for treatment of minors without parental consent (e.g., emergency treatment or treatment of venereal disease), stated that it could find no legislative intent to do away with the need for parental consent. The court went further, however, and also stated that it could not find any policy that would prevent adoption of the mature minor exception. In reaching this decision, the court stressed that the facts of each case should be considered when determining whether or not a minor has capacity to consent.[45] In this instance, the court considered the plaintiff's age, maturity, abilities, demeanor, conduct, and understanding of the nature and risks of the proposed treatment, and found that the minor *did* have the capacity to consent. Thus, the court did not adopt a bright-line, easy-to-follow test.

This wide variety of state schemes adds another layer of complexity into obtaining informed consent in studies involving minors. Many protocols require that parental consent be obtained for subjects under eighteen, yet a requirement in a drug study protocol that all adolescent participants obtain parental consent may be more restrictive

[41] Cardwell v. Bechtol, 724 S.W.2d. 739, 745 (Tenn. 1987) (*citing* Colley v. State, 179 Tenn. 651 (1943)).

[42] *Cardwell*, 724 S.W.2d at 741-42.

[43] *Id.* at 742.

[44] *Id.* Battery "is an intentional and offensive touching of another without lawful justification." BLACK'S LAW DICTIONARY 146 (7th ed. 1999).

[45] *Cardwell*, 724 S.W.2d at 755.

than is warranted in some states. Some of these individuals may have the legal right to consent to participate under their state law. Requiring consent for an emancipated minor may be unnecessary, may be inconsistent with the state's objectives in adopting emancipation laws, and may exclude subjects who have the right to participate.

For example, an emancipated minor may meet all study eligibility criteria except for parental consent; yet the very circumstances that led to the emancipation also may mean that there is no parent or guardian to give consent. Given the difficulty companies often have in recruiting pediatric subjects, an unduly restrictive approach could hamper subject accrual and could even be at odds with a would-be subject's desire to access the potential benefits of study participation.

III. PARTICIPATION BY ADULTS WHO LACK THE CAPACITY TO CONSENT

Pharmaceutical companies also are conducting an increasing number of studies of drugs in adults who have some type of cognitive incapacity. With the aging of the population, this is a rapidly growing subset of the population. Yet, enrolling these subjects in clinical trials presents its own set of informed consent issues.

As is the case for children, the determination of whether an adult has the capacity to consent is based largely on state law. Similarly, state law determines who has the authority to consent for an adult, if the potential subject does not have the ability to consent for him or herself.

Again, there is substantial variation among the states on this issue. Arkansas and New Hampshire expressly forbid surrogate consent for experimental medical procedures without court approval,[46] while other states allow consent by a court-appointed guardian or surrogate,[47] by court-ordered priority list, or by a statutorily-defined consent priority list.[48] A majority of states do not address the issue of consent for research directly. Of those states that do not, most have some type of statute that provides for consent for treatment.

A Maryland statute provides an example of who can consent for an incapacitated patient, organized by order of priority:

> The following individuals or groups, in the specified order of priority may make decisions about healthcare for a person who has been certified to be incapable of making an informed decision and who has not appointed a healthcare agent in accordance with this subtitle. Individuals in a particular class may be consulted to make a decision only if all individuals in the next higher class are unavailable:
>
> (i) A guardian for the patient, if one has been appointed;
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> (ii) The patient's spouse;
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> (iii) An adult child of the patient;
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> (iv) A parent of the patient;
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> (v) An adult brother or sister of the patient; or

[46] ARK. CODE ANN. § 28-65-302 (Michie 2003); N.H. REV. STAT. ANN. 464-A:25 (2003).

[47] *See, e.g.*, ALA. CODE § 26-2A-108 (Michie 2003).

[48] *See, e.g.*, FLA. STAT. ANN. § 765.401 (2003); OKLA. STAT. tit. 63, § 3102A (West 2003).

> (vi) A friend or other relative of the patient who meets the requirements of paragraph (3) of this subsection.[49]

Establishing who has actual authority to consent for an incapacitated person, and then locating the person with that authority, can be an added complication. Documents such as durable power of attorney, advance directives, or living wills may be useful for determining who has authority. Each state, however, may require that specific provisions or language be included or specific forms used in these documents for studies in that state. Whether that document will be recognized in a different state is a separate question.

To determine whether or not an out-of-state document will be accepted in the state in which a clinical trial is conducted requires a review of state law. Colorado has a statute that addressing this issue that specifies that "unless otherwise stated in a medical durable power of attorney, it shall be presumed that the principal intends to have [it] executed ... [and] recognized to the fullest extent possible by the courts of any other state."[50]

Where there is difficulty locating someone with authority to consent to research or to medical treatment of an incapacitated person, or where there are multiple parties with potentially competing claims of authority, state statutes may provide some guidance. A Washington statute specifies that a physician who "makes reasonable efforts to locate and secure authorization" from someone in the first or successive orders of priority without success, may look to any person in the next "order of descending priority."[51] It further states that no one in the priority list will be able to provide consent if someone of a higher order refuses the treatment or if two or more members of the same order do not agree.[52] Unfortunately, the statute does not provide guidance on how to resolve these types of conflict.

In addition, individual state laws may create legal pitfalls of which sponsors need to be wary of when trying to enroll cognitively-impaired subjects. A California statutory provision relates specifically to the protection of subjects who are under a conservatorship and to developmentally-disabled adults. It provides that informed consent by a third person "shall only be for medical experiments related to maintaining or improving the health of the human subject or related to obtaining information about a pathological condition of the human subject."[53] Noncompliance with informed consent requirements can result in fine, imprisonment, or both.

In California, a person "primarily responsible for conduct[ing]" the research who is negligently noncompliant with informed consent requirements is liable for a fine of no less than $50 or more than $1,000.[54] If the person is found "willfully noncompliant," the fine could be as much as $5,000.[55] If the responsible person is "willfully noncompliant" and "knowingly expos[es]" the subject to "substantial risk of harm," the penalty may be imprisonment up to one year, a fine of $10,000, or both.[56] Penalties also can be imposed on persons other than the investigators conducting the research. Pharmaceutical representatives or employees who contract with another person to conduct research, who have knowledge of the "risks or hazards" of the intervention, and who withhold infor-

[49] MD. CODE ANN., HEALTH-GEN. § 5-605(2) (2002).
[50] COLO. REV. STAT. § 15-14-509 (2002).
[51] WASH. REV. CODE § 7.70.065(2) (2003).
[52] *Id.*
[53] CAL. HEALTH & SAFETY CODE § 24175(e) (Deering 2003).
[54] *Id.* § 24176(a).
[55] *Id.* § 24176(b).
[56] *Id.* § 24176(c).

mation about those risks also may be at risk of imprisonment up to one year, a fine of $10,000, or both.[57]

The California statutory requirement that a medical experiment maintain or improve the health of the subject might appear to preclude inclusion of incapacitated subjects in placebo-controlled trials where patients in the placebo group would receive no benefit and arguably, depending on the disease or condition being treated, no maintenance of their condition.

Pharmaceutical study protocols are designed primarily with FDA requirements in mind. It is not clear that all randomized, placebo-controlled, double-masked studies conducted in California with cognitively-impaired adults are designed to maintain or improve the subject's health or to provide information about the potential subject's pathological condition. If these criteria are not met, it is not certain under California law that the third party can provide a valid consent. Unfortunately, California has not adopted any implementing regulations to explicate or clarify this provision.

Similarly, Virginia has its own law defining permissible clinical studies for adults incapable of making an informed decision. Under this law, a legally authorized representative cannot consent to nontherapeutic research unless a human research committee establishes that there will be "no more than a minor increase over minimal risk to the human subject."[58] At a minimum, sponsors should be aware of this and other similar state laws, so that they can make informed judgments as to the applicability of such laws and take steps to enhance compliance.

FDA approval of an IND does not necessarily preempt or overrule state laws. While a pharmaceutical sponsor that is cited for violating a state law may cite IND approval in its favor in the event of a dispute, there is no guarantee that the IND will insulate the company from being deemed to have violated state law.

New York State provides its own potential twist, based on case law.[59] Under a regulation promulgated by the New York State Office of Mental Health (OMH), procedures were established that would allow for the nonconsensual inclusion of mental patients in clinical experiments that potentially could result in harmful, permanent, or fatal side effects.[60]

This provision was challenged by involuntarily-institutionalized patients and patient advocacy organizations as an unconstitutional deprivation of due process under the state constitution. Even though the regulation afforded study subjects protection through eight general prescreening requirements—including one purporting not to deprive the patients of any "rights, privileges and protections"—the court struck down the law. The trial court found in favor of the plaintiffs, holding that the regulation was beyond OMH's statutory authority and was therefore invalid.[61] On appeal, the appellate court affirmed and modified the lower court's judgment, finding that sections of the OMH regulation were a violation of both state and federal due process.[62]

This decision applies directly only to a small number of potential subjects in New York who are protected under a specific provision of state law. Thus, the decision has limited direct impact. Yet, the analysis used by the court potentially applies to clinical studies involving subjects who are involuntary residents at other state-run facilities. In its discussion of the narrow scope of the effect of this decision, the court noted:

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[57] *Id.* § 24176(d).

[58] VA. CODE ANN. § 32.1-162.18(B) (Michie 2002).

[59] *See* T.D. v. New York State Off. of Mental Health, 650 N.Y.S.2d 173 (N.Y. App. Div 1996).

[60] N.Y. COMP. CODES R. & REGS. tit. 14, § 527.10 (repealed 1998).

[61] *T.D. v. OMH*, 650 N.Y.S.2d at 178.

[62] *Id.* at 194.

> [T]he controversy has wide significance since it arises within the larger context of medical research involving human subjects, ... requir[ing] a balancing of [the] State's responsibility to protect individuals who, because of mental illness, age, birth defect, other disease or some combination of these factors, are incapable of speaking for themselves, from needless pain, indignity and abuse, against its worthwhile goal of fostering the development of better methods to diagnose, treat and otherwise care for these same individuals through cooperation with the medical community and private industry.[63]

The *OMH* case also illustrates that standards for evaluating whether informed consent has been provided are set by courts, as well as by state legislatures.

IV. EMERGENCY TREATMENT

Research and development of immediate medical and pharmaceutical interventions for emergent conditions has been difficult for a variety of reasons. One of the many hurdles has been how to obtain informed consent. The principles that underlie the need for consent do not disappear automatically because the potential subject is unconscious and may benefit from immediate investigational therapy.

In many emergent situations, however, the first few hours are critical to the eventual outcome. Administration of the drug may need to occur almost immediately. For example, the product labeling for Activase®, a recombinant tissue plasminogen activator, recommends that treatment be initiated within three hours after the onset of stroke.[64]

When a patient is severely injured or unconscious and cannot consent, waiting for or finding the appropriate surrogate may not be feasible. FDA regulations do provide an exception, when certain conditions are met, from the requirement of informed consent for emergency research.[65] The requirements for this exception can be quite onerous and include, among other things, the need for the local community to be consulted and given the opportunity to participate in the IRB process to approve the informed consent exception. These FDA regulations, while intended to liberalize the consent requirement by providing an alternative pathway, are not easy to meet. And, although considerable agency resources were expended to develop the regulation, it apparently has been used only rarely.

Even if a sponsor can satisfy all of FDA's requirements, that may not be enough, as there is an additional layer of state issues. Not all states have emergency treatment laws conducive to the use of investigational drugs, and the informed consent requirements can be quite diverse.

California permits "medical experimental treatment" if that treatment benefits a patient in a "life-threatening emergency" and if a number of specific conditions—in addition to those required by federal regulations—are met.[66] These state-imposed conditions require that the patient is in a "life-threatening situation necessitating urgent intervention" and that there are no proven or satisfactory alternatives available; that, due to the medical condition, the patient cannot give informed consent; that a legally authorized surrogate for consent cannot be found before the treatment must be given

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[63] *Id.* at 176.

[64] Genentech, Activase®, (Alteplase, recombinant) package insert, online full prescribing information, *available at* http://www.gene.com/gene/products/information/cardiovascular/activase/insert.jsp (last visited June 17, 2004).

[65] 21 C.F.R. § 50.24.

[66] CAL. HEALTH & SAFETY CODE § 24177.5(a).

and the protocol defines the therapeutic timeframe for administration of the treatment; that there is no way to identify patients prospectively for the treatment protocol; and that studies have been done that show the intervention has a potential to benefit the patient.[67] These criteria go well beyond FDA's own regulations.

A New Jersey statute identifies a list of patient rights, including the right "to be advised if the hospital proposes to engage in or perform human research and experimentation and to refuse to participate in these projects."[68] The statute includes an exception for informed consent for "those emergency situations not requiring informed consent," but it is not clear whether this exception means that all emergency research is excluded from the need for informed consent.[69]

As is the case for minors and incapacitated adults, state regulations must be consulted to determine who can provide substituted consent. One significant difference in the emergency research situation is that time is a critical factor. Locating and identifying the person with appropriate authority may not be feasible where time is constrained. State law diversity in defining who can provide substituted consent, and limitations on what they can consent to, further complicates substituted consent for emergency research. When contemplating emergency procedures where substituted consent is needed, the sponsor would be well advised to assess whether the research would raise state law issues and to develop mechanisms to comply (e.g., developing a state-appropriate list of relationships that can provide consent).

V. GENETIC TESTING

State law also plays a significant role in another increasingly-important clinical area, namely genetic screening. Pharmacogenetics and pharmacogenomics are becoming more prevalent and important to clinical research.[70] With the advent of pharmacogenomics, more drug companies are using tissue samples to conduct genetic testing. This testing can raise many ethical, legal, and regulatory issues that are outside the scope of this article, but this is an area where drug sponsors must be particularly attentive to state law. Many states have established regulations regarding informed consent prior to testing, for storage or retention of samples, and for dissemination of genetic test results.

Drug companies will need to be certain that any testing conducted on the subject's tissues is covered by the informed consent form. For example, if the form gives consent to determine whether the HIV virus is present, but the subsequent testing includes HIV genotyping of the subject, this testing may be outside the scope of the informed consent form. The extent to which the informed consent process covers this testing largely will be determined by reference to state law. Similarly, state law will govern whether informed consent is required for, or extends to the storage or retention of, genetic samples. In drafting informed consent forms for prospective trials that may entail future genetic testing, sponsors should ensure that the forms explicitly cover this conduct. Various federal bodies, such as the National Bioethics Advisory Commission,[71] have provided guidance on these types of issues. These views presumably would be given considerable weight in any dispute between the subject and sponsor, but when adjudicating whether there had been valid consent for the use to which a specimen was put, a court probably would deem state law to be decisive.

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[67] *Id.*

[68] N.J. STAT. ANN. § 26:2H-12.8(l) (West 2003); N.J. STAT. ANN. § 30:4-24.2 (West 2004).

[69] *Id.*

[70] R. Weinsbilbaum, *Inheritance and Drug Response*, 348 NEW ENG. J. MED. 529 (2003).

[71] *See* The President's Council on Bioethics, formerly the National Bioethics Advisory Commission, *at* http://www.bioethics.gov/.

Requirements vary widely from state to state. Most states that have laws regarding genetic testing require written consent for performing tests or releasing results. For example, Missouri law requires that, prior to information release, the patient must be fully informed of the scope of the information to be released, the risks and benefits of releasing the information, and the identity of those to whom it will be released.[72] Florida, Colorado, New Mexico, and New Jersey have statutes that describe genetic information or results as the "unique" or "exclusive" property of the person it is taken from. In these states, it is unlawful to "release," "disclose," or "retain" the genetic information without the patient's "written" or "informed" consent.[73] New Mexico's regulation requires the "information or sample" to be destroyed if the patient requests it, except when "retention is authorized under a research protocol approved by an institutional review board (IRB) pursuant to federal law."[74]

New York requires a general description of the genetic test; a statement of the purpose of the test, and a recommendation to seek genetic counseling; a statement that the test may show a predisposition to presence of a disease or condition; a description of each disease or condition being tested; the level of certainty that a positive result indicates predisposition; names of persons to whom the results may be released; a statement that no unconsented to tests will be performed; and the length of time the sample will be retained.[75] Nebraska's law is essentially the same as New York's, except that it does not require a recommendation to seek counseling.

Massachusetts also has its own genetic testing law.[76] Under that statute, a laboratory performing genetic tests must ensure that a written request for any genetic testing is received, that the person ordering the test is authorized to do so, and that the request for the test is accompanied by a statement that the requestor has obtained prior written consent for the test from the person receiving the test.[77] Failure to comply with this Massachusetts law may result in administrative sanctions from the Massachusetts Department of Health, civil action for injunctive or other equitable relief from the state attorney general, or private action for injunctive or other equitable relief from the patient in his or her own name.[78]

These state requirements, to some degree, overlap with FDA informed consent regulations, but they are not identical. A consent form that meets FDA requirements may not satisfy state requirements. Drafting a consent form that satisfies FDA and the various states is no small task. Rather than trying to tailor consent forms for each state, it may be easier to develop a master consent form that incorporates all of the elements of current legislation. Of course, sponsors also need to be aware that in this evolving arena state genetic testing laws and regulations are subject to change, and that state courts can impose requirements as well.

VI. MEDICAL PRIVACY—HIPAA

HIPAA was enacted to ensure health insurance coverage for employees undergoing changes in employment, and to set standards for electronic healthcare information. To

[72] MO. ANN. STAT. § 191.317 (West 2002).

[73] FLA. STAT. ch. 760.40(2)(a) (2002); COLO. REV. STAT. § 10-3-1104.7 (2002); N.M. STAT. ANN. § 24-21-5 (Michie 2002); N.J. STAT. ANN. § 10:5-47(a).

[74] N.M. STAT. ANN. § 24-21-5(b)(3) (Michie 2003).

[75] N.Y. CIV. RIGHTS LAW § 79-1(2) (Consol. 2003).

[76] MASS ANN. LAWS ch. 111, § 70G (Law. Co-Op. 2000).

[77] *Id.*

[78] *Id.*

address concerns about the effect of electronic technology on private healthcare information, HIPAA also included provisions that establish a national policy and standards for the privacy of identifiable health information. With the passage of HIPAA, protecting the privacy rights of patients is emerging as one of the major issues in medicine. DHHS-issued regulations to protect the confidentiality of medical records are finally in effect.

HIPAA is extraordinarily complex and confusing,[79] and this article will only briefly summarize this remarkably abstruse topic. Under HIPAA, the general rule prohibits a "covered entity" (CE) from using or disclosing any "protected health information" (PHI).[80] CEs are healthcare providers, including investigative sites, that transmit healthcare information. PHI is information, stored or sent in any form, that relates to the physical or mental health of an individual, the medical care given, or the payment for healthcare, if that information can be used to identify the individual. Sites will be liable if they disclose PHI (e.g., in research data) to a sponsor without the proper authorization.

To comply with HIPAA, an investigative site should not use or disclose PHI without valid subject authorization. This authorization may be combined with the consent to participate in a trial, but should be in a separate section of the form, with a separate signature. The authorization should state what PHI will be disclosed, and to whom; why the information will be used or disclosed; an expiration date (may be undefined as in "end of the study"[81] or open-ended as in "none"[82]); and a statement giving the patient the right to revoke the authorization. Treatment that is part of the research may be conditioned on continued authorization.[83]

HIPAA represents the minimum federal requirements; however, state regulations may be more stringent than those established under HIPAA. HIPAA preempts only those state regulations that are less restrictive than the privacy rule. If a state law is contrary to a provision in the privacy rule, and the state law is more stringent, the state law prevails. If a state law and HIPAA are not contrary, a sponsor may have to comply with both laws.

Many states have adopted their own privacy laws. New York has adopted a particularly stringent provision. Under HIPAA, PHI for "treatment, payment, or healthcare operations" may be sent to another CE without the consent of the patient, "as required by law."[84] New York, however, permits "copies of all ... medical records ... regarding that patient to any other designated physician or hospital [only] [u]pon the written request of the [patient]."[85] The New York law prevails over HIPAA because it is more stringent and it is "required by law." New York's stricter requirements on the exchange of information may have an effect on some activities related to patient accrual, such as prescreening and data review.

Texas also has more stringent requirements than those defined in HIPAA, in that Texas' definition of CE is broader than that of HIPAA. A covered entity in Texas is defined to include "any person who ... (A) engages in ... the practice of assembly, collecting, analyzing, using, evaluating, storing or transmitting; (B) comes into posses-

[79] Jeffrey Wasserstein & Alan Kirschenbaum, *HIPAA and Drug Company Interactions With Physicians—Beyond Clinical Research*, FDLI UPDATE, May/June 2003, at 37.

[80] 45 C.F.R. § 164.502.

[81] Standards for Privacy of Individually Identifiable Health Information, 67 Fed. Reg. 14,776, 14,813 (Mar. 27, 2002).

[82] *Id.* If the data or information may need to be re-examined at a later time, reauthorization will be required unless the expiration date is "none."

[83] 45 C.F.R. § 164.508(b)(4)(i).

[84] *Id.* §§ 164.506(A), 164.501.

[85] N.Y. PUB. HEALTH LAW § 17 (Consol. 2003).

sion; (C) obtains or stores PHI [or] is an employee, agent, or contractor of a person described [in] paragraphs (A), (B), or (C)."[86] HIPAA defines a covered entity to include "a health plan[,] healthcare clearinghouse[, or] healthcare provider who transmits any health information in electronic form in connection with a transaction covered by this subchapter."[87] The Texas definition is broader because it can be read to extend the definition of a CE to the sponsor of a clinical trial.

California has its own unique requirement regarding the release of medical information. In September 2003, a state law was enacted that specifies that valid authorization to release medical information must be "handwritten by the person who signs it ... [or] is in a typeface no smaller than 14-point type."[88] California also has a regulation requiring that written patient materials (including consent for admission and treatment) provided by acute and intermediate care hospitals, skilled nursing facilities, and residential care facilities be, at a minimum, in 12-point font.[89] Trial sponsors and investigators will need to decide whether to use two different size fonts in their patient materials, or default to the 14-point font required for the release of medical information. To remain in compliance with state and federal privacy requirements, sponsors, investigators, and investigator sites will need to be familiar with even the smallest details of the applicable state privacy laws.

VII. UNIQUE STATE LAWS

A. *HIV*

A number of clinical research protocols require that research participants receive an HIV test before participating in studies. Unless the participants' HIV status will truly affect the outcome of the study, sponsors and researchers should consider carefully the importance of obtaining participants' HIV status. Simply requesting and obtaining that test result triggers a number of state laws.

The vast majority of states require informed consent before an HIV test can be performed. A majority of states place the burden of obtaining informed consent on the physician ordering the test. Several states also strictly define what constitutes "informed consent" for an HIV test. Arizona and Michigan are among the states that define informed consent to include the patient's understanding of the purpose of the test, the meaning of the result, and the confidentiality requirements of that result.[90] Other states, including Colorado, Delaware, Iowa, Maryland, and New York, also require that the physician ordering the test inform the patient of the causes and symptoms of AIDS and provide information about the behaviors than can lead to HIV infection.[91] There appears to be no exemption to this merely because the test is performed in conjunction with clinical research. Most states require that informed consent be in writing, but in Louisiana and Ohio, informed consent for an HIV test can be communicated orally.[92]

Delaware and North Carolina do provide exceptions to the informed consent requirement if the HIV test is taken for the purpose of participation in a clinical research study.

[86] TEX. HEALTH & SAFETY CODE ANN. § 181.001 (Vernon 2003).

[87] 45 C.F.R. § 160.103(3).

[88] 2003 Bill Text CA A.B. 715.

[89] CAL. HEALTH & SAFETY. CODE § 123222.1.

[90] *See* ARIZ. ADMIN. CODE § 36-663 (2003); MICH. STAT. ANN. § 333.5733 (2003).

[91] *See* COLO. REV. STAT. § 10-3-1104.5(3) (2003); DEL. CODE ANN tit. 16, § 1202(b) (2003); IOWA CODE § 141A.7 (2003); MD. HEALTH-GENERAL CODE ANN. § 18-336 (2002); N.Y. CRR tit. 10 § 63-3 (2003).

[92] *See* LA. REV. STAT. ANN. § 1300.13 (West 2003); OHIO REV. CODE ANN. § 3701.242 (Anderson 2003).

In Delaware, informed consent for an HIV test is not required if "the testing is done for the purposes of research; provided that the test is performed in a manner by which the identity of the test subject is not known and may not be retrieved by the researcher."[93] North Carolina's exception is even broader; in that state, informed consent does not apply to an HIV test "performed solely for research purposes under the approval of an institutional review board."[94] These states, though, are the exceptions; generally, state HIV testing laws apply even to clinical investigations.

Once an HIV test has been administered, the test result—and in most states, the fact that the test was even performed—is confidential. All fifty states have regulations preventing laboratories, physicians, and other healthcare professionals from releasing the results of HIV tests without the written consent of the subject. In many states, healthcare professionals face criminal penalties for disclosing HIV test results without the patient's written authorization. Further, every state requires that a positive HIV test result be reported to the state health department or other public health agency. Hawaii, Illinois, Iowa, New York, and Virginia are among the states that place this reporting burden on the physician who ordered the HIV test.[95] The physicians who ordered the HIV test also may be required to provide face-to-face counseling about the meaning of the test result, behavior modification to prevent transmission, and the importance of contacting individuals who may have been exposed to HIV through sexual contact and intravenous drug use.[96] Physicians in Maryland and Pennsylvania are required to help HIV-positive patients contact individuals who may be infected.[97]

B. *Physician Payments*

Payments to investigators may present other state law issues. FDA requires disclosure to the agency of certain types of payments,[98] but does not restrict sponsor-investigator financial arrangements. Compliance with the applicable FDA regulation, however, does not obviate state law issues. The American Medical Association (AMA) has issued an Ethics Opinion dealing with the financial stake of investigators. The AMA has established seven guidelines, including one dealing with disclosure of financial incentives to subjects and another relating to differentiation "between the physicians' roles as clinician and investigator."[99]

These AMA Code of Ethics provisions may be more than wishful ethical aspirations. At least four states have determined that violation of AMA's Code of Ethics is unprofessional conduct,[100] which apparently could mean that a clinical investigator who violates an Ethics Opinion faces the possibility of state sanctions. A finding by a state medical board that an investigator acted unethically presumably would not directly affect the sponsor, but this finding would complicate a sponsor's efforts to exonerate

[93] DEL. CODE ANN. tit.16 § 1202(c)(2) (2003).

[94] N.C. GEN. STAT. § 13A-148 (2003).

[95] *See* HAW. REV. STAT. ANN. § 325-101 (Michie 2003); 410 ILL. COMP. STAT. 325/4 (2003); IOWA CODE § 141A.5 (2003); N.Y. CLS PUB. HEALTH § 2130 (2003); VA. CODE ANN. § 32.1-36 (Michie 2003).

[96] These requirements are placed on physicians in Alabama, Iowa, Maine, Maryland, New York, Pennsylvania, and Washington. *See* ALA. CODE § 22-11A-53 (2003); IOWA CODE § 141A.5; ME. REV. STAT. ANN. tit. 5, § 19204-A (Michie 2003); MD. HEALTH-GENERAL CODE ANN. § 18-336 (2002); N.Y. CLS PUB. HEALTH § 2781; 35 P.S. § 7605; and WAC § 246-100-207.

[97] *See* MD. HEALTH-GENERAL CODE ANN. § 18-336; 35 P.S. § 7605.

[98] 21 C.F.R. pt. 54.

[99] *See* American Med. Ass'n, E-8.0315 Managing Conflicts of Interest in the Conduct of Clinical Trials, *available at* http://www.ama-assn.org/ama/pub/category/8471.html (last visited June 21, 2004).

[100] *See* JOHN M. ISIDOR & SANDRA P. KALTMAN, IMPLICATIONS OF AMA'S ETHICS OPINION ON MANAGING CONFLICTS OF INTEREST IN CLINICAL TRIALS (BNA 2003).

itself if the company were sued over injuries caused by that investigator's failure to obtain the subject's consent, or for other reasons.

C. *Enrollment Incentive/Referral Fees*

Clinical studies do not always enroll subjects as quickly as desired. To encourage subject recruitment, sponsors sometimes will offer financial incentives to investigators. Depending on the circumstances, this can raise a variety of questions, including whether the subjects were adequately advised of any conflicts of interest. Their conduct also may raise state law issues.

Many states prohibit physicians from receiving financial incentives for patient referrals.[101] California enacted a law specifically to protect the public from increasing healthcare costs and from referrals based on considerations other than the best interest of the patient.[102] Although the law provides special exceptions for referrals to laboratories, clinics, and other physicians for diagnostic tests and care, its prohibitions have been extended by the state's Attorney General to clinical research programs. In 1993, the California Senate asked the state Attorney General for an opinion as to whether a pharmaceutical company sponsoring a clinical research program could pay referral and evaluation fees to physicians for referring their patients to the program and evaluating the results.[103]

In the program at issue, the pharmaceutical company paid patients for their participation and provided them with free drugs, medical care, and laboratory services. The California Attorney General determined that, under California law, physicians could not be paid referral fees for referring their patients to the research program.[104] Quoting a 1967 California Appeals Court decision, the Attorney General emphasized that a "patient deserves to be free of any reasonable suspicion that his doctor's judgment is influenced by a profit motive."[105] Violation of this provision may be punishable by up to one year in prison, a $50,000 fine, or both.[106]

The Attorney General's opinion stressed that the physician referring a patient to the research program was the only person who could determine whether participation was in the patient's best medical interest.[107] According to the Attorney General, this judgment could be clouded by pecuniary interests.[108] Physicians in California, however, are still permitted to receive evaluation fees for legitimate evaluations of research program results.[109]

D. *California Research Advisory Panel*

Another potential complication when conducting clinical research in California is the Research Advisory Panel of California. California requires that proposed research projects involving certain controlled substances be prereviewed and approved by the Research Advisory Panel.[110] This panel, which consists of representatives of the Attorney Gen-

[101] *See* CAL. BUS. & PROF. CODE § 650 (Deering 2003).

[102] *See* 76 Op. Atty. Gen. Cal. 204, 1993 Cal. AG LEXIS 34, at *3 (1993).

[103] *See id.* at *1.

[104] *See id.*

[105] *Id.* at *4 (quoting Magan Medical Clinic v. Cal. State Bd. of Med. Examiners, 249 Cal. App. 2d 124, 132 (1967).

[106] CAL. BUS. & PROF. CODE § 650.

[107] *Id.* at *7.

[108] *Id.*

[109] *Id.* at *1. The California Supreme Court also held that subjects may have a claim against investigators who had an undisclosed conflict of interest. Moore v. Regents of Univ. of Cal., 51 Cal. 3d 120 (Cal. 1990).

[110] *See* CAL. HEALTH & SAFETY CODE § 11213.

eral, the State Department of Health Services, the California State Board of Pharmacy, a pharmacologist or physician from the University of California, and other health professionals, meets six times per year to review human subject research involving Schedule I and Schedule II controlled substances or research for the treatment of abuse of any drug, scheduled or not.[111] California law mandates that the lead investigator of studies fitting either of these categories obtain Research Advisory Panel approval prior to beginning the study.[112] Under California regulations, the Research Advisory Panel may withdraw its approval of a research project "at any time."[113]

California regulations seem to grant the Research Advisory Panel the authority to approve clinical research studies involving Schedule I and Schedule II drugs, but it is uncertain whether the Research Advisory Panel has any real power. The Research Advisory Panel would seem to be aware only of the research studies that are submitted; it is unclear whether the body is able to prevent or halt research studies that are never presented to it. Apparently, this body has never invoked whatever regulatory powers it may possess. Nevertheless, there are examples of long-dormant state regulatory bodies that "awaken" and take enforcement action.

VIII. IMPLICATIONS OF NONCOMPLIANCE WITH STATE LAW

Many pharmaceutical studies involve patient populations that are unlikely to implicate unique state requirements, and compliance with the informed consent standards set out in 21 C.F.R. Part 50 will satisfy all of the applicable legal standards. This, however, is not uniformly the case. Many studies potentially will raise issues relating to conformance with state-established informed consent requirements.

A natural question is whether these state law issues are of any practical concern to drug sponsors. FDA is the proverbial "800-pound gorilla" in the oversight of pharmaceutical trials. FDA can take enforcement actions for noncompliance, and can reject applications. In light of FDA's prominence, is there any reason for sponsors to be concerned about compliance with state law? The answer is yes. Violations of state law can carry a variety of potential penalties. For example, a drug company that fails to comply with California's statute regulating pharmaceutical clinical trials can be fined up to $5,000. While this amount may be comparatively small, the ancillary consequences may be much greater.

Nonconformance with state provisions can have implications at the federal level. FDA regulations require that informed consent be obtained. Thus, if a minor is improperly enrolled in a clinical trial, or a cognitively impaired adult is enrolled without proper authorization by a third party, the sponsor potentially has violated FDA's informed consent requirements, albeit indirectly. This can lead to enforcement action against the sponsor, and may cast a shadow over the acceptability of the data. FDA reserves the right to reject marketing applications in which valid consent is lacking.[114] In reality, the agency is unlikely to reject an otherwise safe and effective drug due to noncompliance with state law requirements. If the sponsor uses the improperly-collected data to support a marketing application, however, FDA is not precluded from issuing a warning letter to the sponsor or investigator, or taking other action due to the violation.

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[111] *See* CAL. HEALTH & SAFETY CODE §§ 11480, 11481.

[112] *See id.* §§ 11480, 11481. *See also* UC Irvine Research and Graduate Studies, State Requirements for Research Using Controlled Substances, *available at* http://www.rgs.uci.edu/researchprotections/irb/controlledsubstances.htm (last visited June 23, 2004).

[113] CAL. HEALTH & SAFETY CODE § 11481.

[114] 21 C.F.R. § 314.50 (c)(ix).

Most worrisome, perhaps, is the possibility that nonconformance with state law could result in civil liability exposure. Historically, the number of lawsuits involving clinical research is fairly low, but that has changed recently. As the result of some well-publicized mishaps in clinical research, many more lawsuits have been brought.

One recent lawsuit involving an artificial heart, for example, specifically alleged that there had been inadequate informed consent.[115] The wife of a fifty-two-year-old man who died following the artificial heart implant claimed that the investigators knew or should have known that her husband was particularly vulnerable. She claimed that the consent information that they had been given was misleading because the information understated the risks and overstated the benefits of the procedure, failed to inform him of the pain and suffering that he would experience, failed to inform him of the limited benefits of the procedure, and failed to disclose the risks of the experiment. All of these claims arose under state law.

Complaints recently filed in state courts have attempted to extend liability to IRBs, as well as to individual agents and employees of IRBs.[116] *Scheer v. Burke*, filed in Pennsylvania on behalf of a deceased trial participant, sought civil damages from the physician who enrolled the participant in the clinical study, physician and nurse investigators who participated in the clinical study, the hospital at which the clinical study was conducted, the IRB that approved the clinical study, and the individual chairman of the IRB.[117] The participant's widow claimed that the consent process in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Clinical Trial (ALLHAT) was misleading and "materially deficient."[118] According to the complaint, the consent forms failed to name the second- and third-line drugs to be used, and did not disclose the potential serious adverse reactions from these drugs. Additionally, the complaint alleged that the benefits of the study were overstated, while the statement of the risks was misleading and minimized.[119]

During the ALLHAT study, a physician-investigator allegedly dismissed adverse reactions that, pursuant to the study's Manual of Operations, should have prompted blood tests and discontinuation of the study drugs.[120] Investigators reportedly recorded these adverse reactions in the participant's chart, but failed to report them to the ALLHAT Safety Monitoring Board.[121] According to the complaint, while continuing the study drugs, the participant presented renal insufficiency, progression of cataracts, and abnormal ECGs, and also developed drug-induced lupus. The complaint alleged that the participant died from the drug-induced lupus and end-stage glomularnephritis brought on by the study drugs.[122]

Defendants, including the IRB and the individual chairman of the IRB, were sued for wrongful death, lack of informed consent, battery, common law fraud, intentional misrepresentation, and breach of fiduciary duty. Under these claims, the IRB and its chairman were included with other defendants for not adequately monitoring, testing, and treating the participant's condition during the ALLHAT study;[123] for failing to inform

[115] Quinn v. Abiomed, Inc., No. 001524 (Ct. Com. Pl. Phil. Co. 2002).

[116] *See* Scheer v. Burke, No. 000375 (Ct. Com. Pl. Phil. Co. 2003) [hereinafter *Scheer* Complaint]; Hamlet v. Genentech, No. 03 CVS 1161 (Super. Ct. Orange Co. 2003) [hereinafter *Hamlet* Complaint].

[117] *See Scheer* Complaint, *supra* note 116 (case still pending). The complaint contains only the plaintiff's version of events.

[118] *Id.* at 6.

[119] *See id.* at 6-7.

[120] *See id.* at 8-10.

[121] *Id.* at 9.

[122] *Id.* at 11.

[123] *See id.* at 13.

the patient of the risks of all treatment, care, therapy, and medications;[124] and for knowingly misrepresenting the study.[125]

The IRB and its chairman also were sued for negligence. The complaint alleged that the parties who approved the experiment had a duty to protect the participant from unethical research practices.[126] According to the widow, the IRB and its chairman were negligent in "approving the design of the study, in approving the informed consent document, and in not appropriately monitoring the informed consent process and the conduct of the trial."[127] The complaint alleged that this negligence was the direct and proximate cause of the participant's suffering and wrongful death, as well as his heirs' suffering.[128] All of these claims are based on state law.

A North Carolina complaint filed by a clinical study participant brought claims against an IRB for negligence, breach of fiduciary duty, common law fraud, and intentional misrepresentation, as well as claims for constructive fraud and negligent misrepresentation.[129] The patient suffered from psoriatic arthritis, and was enrolled in a double-blind, placebo-controlled, multicenter study to test the safety and efficacy of an experimental drug for patients with plaque psoriasis.[130] The crux of the plaintiff's complaint is that he should not have been allowed to participate in the study because of the arthritic component of his condition.

The complaint sought civil damages against the IRB, as well as other defendants, for not properly examining the participant to determine whether he was an appropriate candidate for the experiment.[131] The complaint alleged that the IRB was careless, negligent, and reckless for not considering the participant's arthritis before allowing him to be enrolled in the experiment and for not monitoring his condition during the study.[132] The IRB also was accused of negligence, breach of fiduciary duty, and misrepresentation because it did not properly inform the participants of the risks associated with the study, nor did informed consent form state that individuals diagnosed with psoriatic arthritis should not participate in the study.[133] Again, these are state-based claims that will be evaluated under state law.

As research expands into segments of the population that are more vulnerable, and thus may be less able to give meaningful consent, the risks relating to the adequacy of consent under state law also potentially expand. Failure to obtain proper informed consent from a minor's guardian, even absent injury, may give rise to some liability exposure for a sponsor. Failure to obtain valid informed consent prior to a medical procedure can be a tort of "battery" under state law, and damages may be awarded for "this unconsented touching." The lack of consent can result in a verdict for the plaintiff, even without any physical harm.

State law liability also can be triggered in other ways. *Greenberg v. Miami Children's Hospital Research Institute, Inc.* illustrates "a tale of a successful research collaboration gone sour."[134] According to the complaint, the plaintiffs had provided biological

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[124] *See id.* at 16.

[125] *See id.* at 18.

[126] *Id.* at 19.

[127] *Id.* at 20.

[128] *Id.*

[129] *See Hamlet* Complaint, *supra* note 116.

[130] *Id.* at 4.

[131] *See id.* at 12.

[132] *Id.* at 12-13.

[133] *Id.* at 8, 13, 14-16.

[134] Greenberg v. Miami Children's Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064, 1064 (U.S. Dist. 2003).

specimens, financial support, and information identifying families with Canavan Disease, a relatively rare genetic disorder. Plaintiffs also alleged that, unbeknownst to them, the defendants had obtained a patent covering the gene for Canavan Disease. The plaintiffs then sued the hospital and the physician-researcher, alleging violations of state law.

The plaintiffs claimed six separate violations of Florida law, including lack of informed consent, breach of fiduciary duty, and unjust enrichment. The court dismissed five counts, but allowed the unjust enrichment count to stand. Although defendants argued that they had invested considerable effort to commercialize this technology, the court noted that the plaintiffs also had invested in the effort. Distinguishing this from the more common research situation, the court noted that plaintiffs had "alleged more than just a donor-donee relationship."[135] Rather, said the court, "the facts paint a picture of a continuing research collaboration that involved Plaintiffs also investing time and significant resources in the race to isolate the Canavan gene."[136]

Although the *Greenberg* case involved neither a drug study nor the typical sponsor-subject relationship, it offers an important lesson: depending on the nature of the pharmaceutical study and the level of the subject's participation (e.g., a lengthy study entailing greater personal subject participation), the study relationship may evolve into one that is viewed as more collaborative. When there is a dispute between the subject and sponsor as to whether the subject is entitled to additional compensation, as was the case in *Greenberg*, the court almost certainly will turn to state law—not FDA regulations—to resolve the issue.

If injury is sustained during a study and the subject did not validly consent, a jury may be more inclined to award a significant sum to the plaintiff. Liability exposure can increase dramatically if a study drug is riskier than expected, if subjects suffer adverse effects, and if there was a violation of a state law designed to protect the well being of research subjects. Plaintiffs' lawyers in a class action lawsuit are likely to latch on to a sponsor's failure to comply with state law as one of the claims in such a suit. A charge that a company conducted unlawful "experimentation" and violated a state law designed to protect vulnerable subjects may well strike a chord with a jury.

In the event of such litigation, sponsors may be able to raise many defenses, including the fact that consent was secured properly. The issues in such a case may be quite complex. A sponsor can argue forcefully that it is the investigator's—not the sponsor's—responsibility to ensure compliance with state law. The investigator has direct contact with the subject, has the obligation to explain the study to subjects, and is in the best position to know whether local law has been satisfied. A sponsor can point out that consent is a process, and that investigators are uniquely positioned to ensure that this process was conducted correctly. Moreover, pharmaceutical investigators commit in writing that they will obtain informed consent.[137] These arguments may prevail with the judge or jury. Allegations of negligence in clinical research do not always prevail, even when patients die.[138]

If a lawsuit is filed relating to a clinical study in which an improperly consented subject suffered injuries (or where there were violations of other state research-related

[135] *Greenberg*, 264 F. Supp. 2d at 1072.

[136] *Id.*

[137] 21 C.F.R. § 312.53 (c)(vi)(d).

[138] *See* Tracy Johnson, *Jury Sides with Hutch, Doctors in Deaths of 5*, SEAT. P.I. REP., Apr. 9, 2004, *at* http://seattlepi.nwsource.com/local/168391_hutch09.html (jury finds for defendants in suit alleging five leukemia patients had not been adequately apprised of the risks of participating in cancer research).

laws), however, the sponsor is not likely to be overlooked when the plaintiff is casting about for defendants to hold accountable. Given that sponsors often have the deepest pockets and that FDA's regulations do impose obligations upon sponsors with respect to informed consent,[139] companies should not completely ignore the threat of litigation based on noncompliance with state law requirements relating to clinical research.

IX. CONCLUSION

In conducting pharmaceutical clinical trials in the United States, sponsors need to comply with a myriad regulatory requirements. Clearly, the most important requirements are those established by FDA. The failure to satisfy FDA's requirements may preclude approval of the product application, and may well have other significant regulatory consequences.

Sponsors, however, should not ignore the potential role of state requirements. Some states have adopted their own statutes regulating informed consent in clinical trials. Moreover, states play a pivotal role in determining whether a subject legally can give valid consent, and, if not, who can consent for them instead. State law also will set the criteria for evaluating whether a specific subject did, in fact, consent. States also have promulgated their own laws and regulations governing genetic testing, privacy, and clinical research. As drug companies devote greater resources to studies in minors, patients with compromised mental functioning, and other individuals whose ability to give valid consent may be called into question, they also should give greater consideration to developing mechanisms to ensure compliance with the various state informed consent requirements. Sponsors need to consider whether multiple states' laws might apply to their investigation (e.g., laws regulating genetic testing, privacy of medical records, HIV testing, emergency treatment, or controlled substances).

Some state requirements may be vulnerable to a preemption challenge;[140] even if some provisions could be challenged, however, many state law requirements are not in conflict with federal requirements. Indeed, in some areas FDA relies upon the states to establish the standards, and states in some circumstances are permitted to impose more stringent requirements. Thus, companies should not make the risky assumption that FDA exclusively occupies the entire field of pharmaceutical clinical research.

The United States has a strong federal system of government and a strong central agency that regulates pharmaceutical research. While FDA is, by far, the most important regulatory body for drug sponsors, it is not the only one. The states matter, too.[141]

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[139] 21 C.F.R. § 312.23(f).

[140] Dowhal v. Smithkline Beecham Consumer Healthcare, 88 P.3d 1 (Cal. 2004) (finding that certain warnings mandated by proposition G5 were preempted).

[141] In *April 1865*, Jay Winik describes how the Civil War definitively and finally determined that there is one United States, as many independent states. JAY WINIK, APRIL 1865: THE MONTH THAT SAVED AMERICA (2001). Even though the vision of a single unified nation prevailed, the states do retain considerable autonomy in the field of pharmaceutical clinical research.